Mathematical Methods for Systems Biology

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Abstract

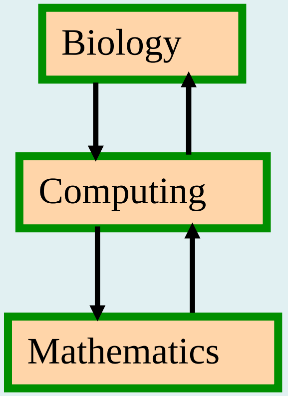
- The tutorial will present a systematic approach to the mathematics of systems biology, reviewing relevant aspects of statistical mechanics, generating functions, operator algebras, stochastic simulation algorithms, network graph structure, graph grammars, cell complexes, and parameter inference. Application examples will be drawn from multiple spatial and temporal scales: bacterial metabolism, eukaryotic transcriptional regulation and signal transduction, and the developmental biology of plants including phyllotaxis.

Useful Physical Mathematics

- Classical mechanics
  - Solid, fluid mechanics
- Statistical mechanics
  - Allosteric enzymes, transcription reg, complexes
  - Image analysis
- Network dynamics
- Field theory
  - Stochastic processes via operator algebra
  - Dynamical Grammars modeling language
  - Multiscale, variable-structure modeling
- Future - extended objects
  - Algebraic geometry
  - Stat mech of membranes

Outline: Math. Methods

- Statistical Mechanics
  – SM in metabolism, transcription
- Stochastic Dynamics
  – Operator algebra
- Classical Spatial Dynamics
  – Hybrid systems; elastic dynamics
- Computational Dynamics
  – Semantics
  – Computational Morphodynamics



Methods

- Partition function algebra
- Composition principle (EMCC)
- Random Steady State (RSS) model

Stat mech review

- Equilibrium stat mech:

$$Z(\beta) = \sum_I \exp(-\beta G_I) \quad \Rightarrow \quad p_I = \exp(-\beta G_I)/Z(\beta)$$

Z is the "partition function". Terms are relative probabilities.

- Nonequilibrium stat mech:

$$\frac{dp_I(t)}{dt} = \sum_J K_{IJ} p_J(t) - \left(\sum_J K_{JI}\right) p_I(t) \equiv \sum_J W_{IJ} p_J(t)$$

- …= 0 for *steady state*
- *Detailed balance:*

$$\frac{K_{IJ}}{K_{JI}} = \frac{p_I^*}{p_J^*} \equiv \exp(-\beta(G_I - G_J))$$

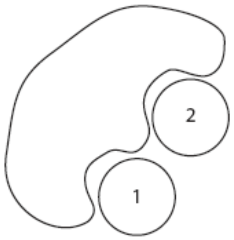
  - Applies to fundamental or closed systems
  - Equilibrium SM is W's leading eigenvector

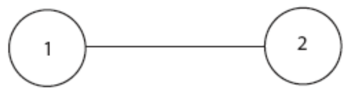
BRIEFINGS IN BIOINFORMATICS.

July 18, 2007

Elementary Partition Functions

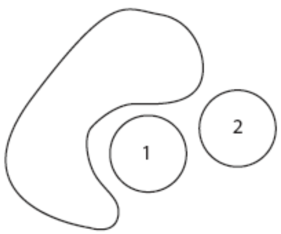
in dilute solution

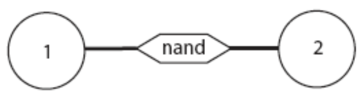




$$Z(z_1, z_2) = \sum_{\{s \,|\, s_i \in \{0,1\} \wedge P(\boldsymbol{s})\}} z_1^{\,s_1} \, z_2^{\,s_2} \, \omega_1^{\,s_1} \, \omega_2^{\,s_2} \, \omega_{1\,2}^{\,s_1\, s_2}$$

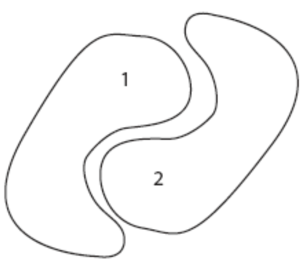
$$= \boxed{1 + \omega_1 \, z_1 + \omega_2 \, z_2 + \omega_{1\,2} \, z_1 \, z_2}$$

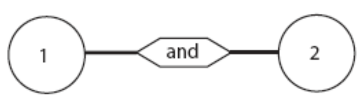




$$P(\boldsymbol{s}) = \overline{s_1 \wedge s_2}$$

$$Z(z_1, z_2) = \boxed{1 + \omega_1 \, z_1 + \omega_2 \, z_2}$$





$$P(\boldsymbol{s}) = s_1 \wedge s_2$$

$$Z(z_1, z_2) = \boxed{\omega_{1\,2} \, z_1 \, z_2}$$

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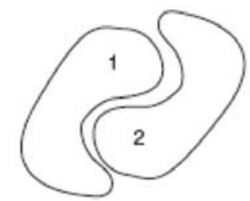
Four principles of partition function algebra

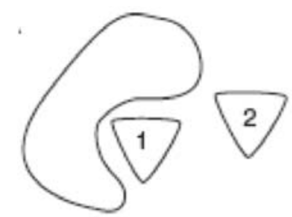
P1. Multiplication ~ independence

$$Z(z_1, z_2) = \omega_{12}\, z_1\, z_2$$



P2. Addition ~ mixture distribution

$$Z(z_1, z_2) = 1 + \omega_1\, z_1 + \omega_2\, z_2$$



P3. Composition ~ tree structure

$$Z_{trimer}(z_1, z_3) = (\omega_1 z_1 + \omega_3 z_3)^3 = \sum_{n_1=0}^{3} \binom{3}{n_1} (\omega_1 z_2)^{n_1} (\omega_3 z_3)^{3-n_1}$$

P4. Contraction ~ cycles

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Methods

- Partition function algebra
- Composition principle (EMCC)
- Random Steady State (RSS) model

Birth and Death Process

- In discrete time: $$g_1(z) = \sum_n p_1(n)\, z^n \;=\; \delta + \gamma\, z + \beta\, z^2$$
$$\gamma = 1 - \beta - \delta$$

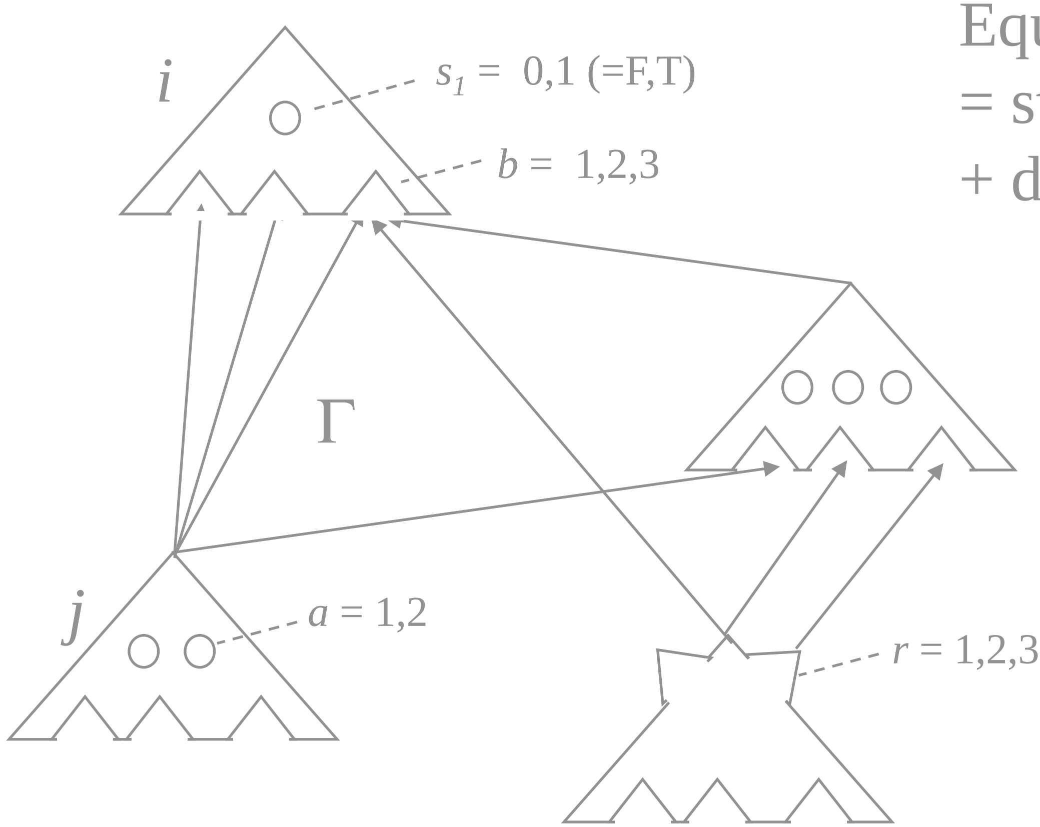
$$g_2(z) \;=\; \delta + \gamma\, g_1(z) + \beta\,(g_1(z))^2 \;\; = g_1(g_1(z))$$

$$= \delta(2 - 2\,\beta - \delta) + (1 - \beta - \delta)\,(1 + \beta - \delta)\, z + \beta\big(2 - 3\,\beta - 3\,\delta + (\beta + \delta)^2 + 2\,\delta\beta\big)\, z^2$$
$$+ 2\,\beta^2 (1 - \beta - \delta)\, z^3 + \beta^3\, z^4$$

$$g_k(x) = g_1(g_{k-1}(x))$$
$$= g_1 \circ g_1 \circ \ldots \circ g_1(z) \quad (k \text{ occurences of } g_1)$$

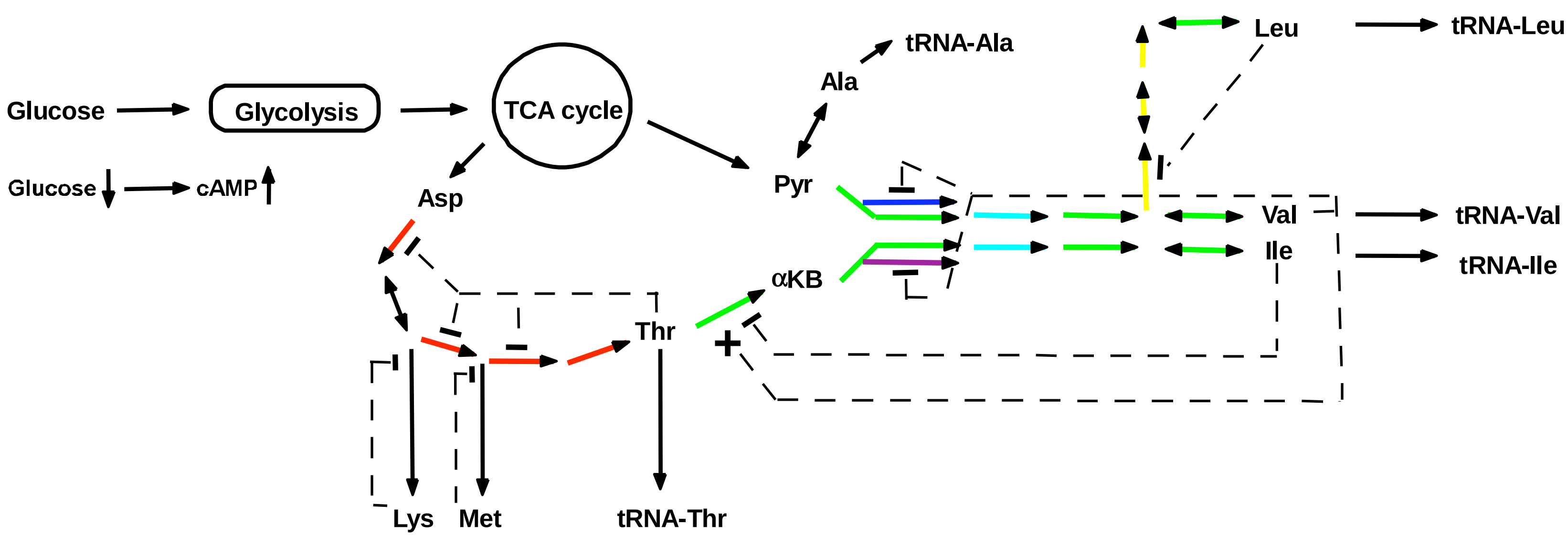
EMCC Picture

Equilibrium Molecular Complex Composition



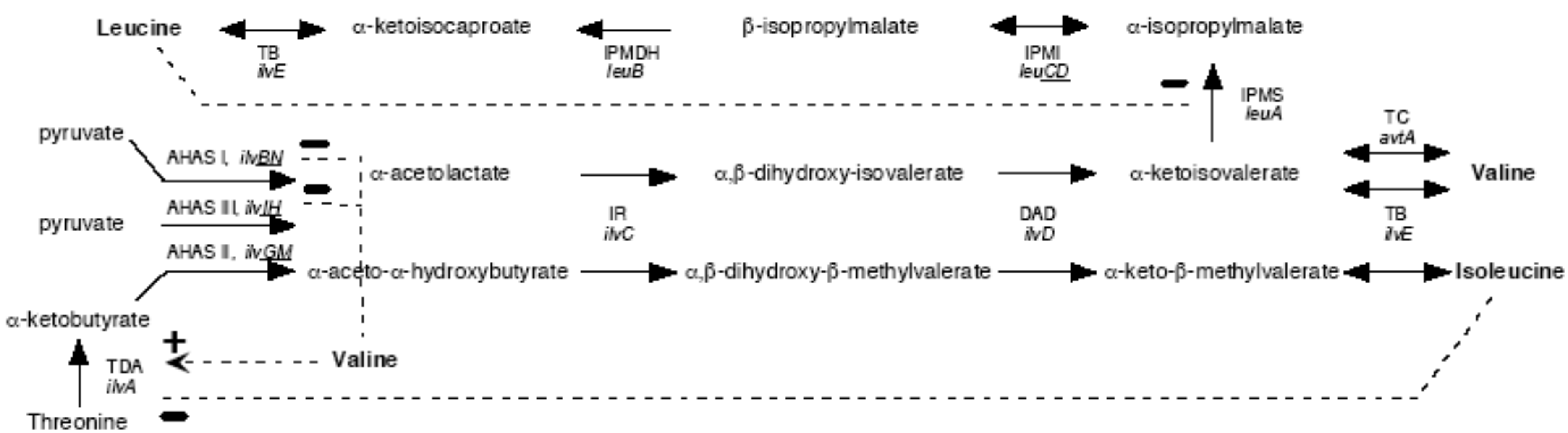
Equilibrium
= steady state
+ detailed balance

Amino Acid Syntheses



Kmech and (Val, Leu, Ile) biosynthesis: Yang, Shapiro, Hung, Mjolsness *Bioinformatics* 21: 774-780, 2005.
Thr biosynthesis from Asp: Najdi, Shapiro, Hatfield, and Mjolsness, *Journal of Bioinformatics and Computational Biology*, 4:335-355, 2006.

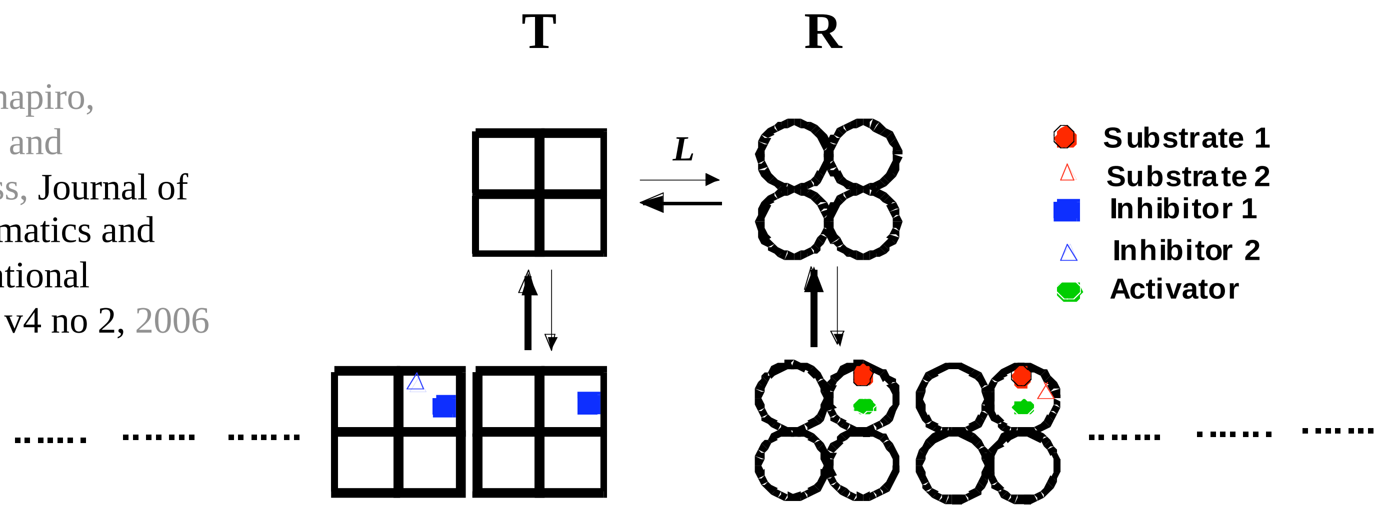
Biosynthesis of Valine, Leucine and Isoleucine



EMCC example: Generalized MWC (GMWC) Model

for multiple substrates, inhibitors and activators

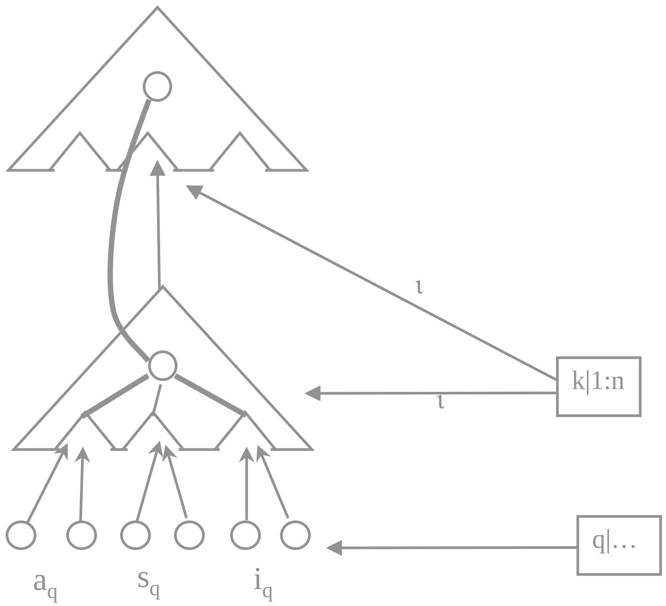
Najdi, Shapiro, Hatfield, and Mjolsness, Journal of Bioinformatics and Computational Biology, v4 no 2, 2006

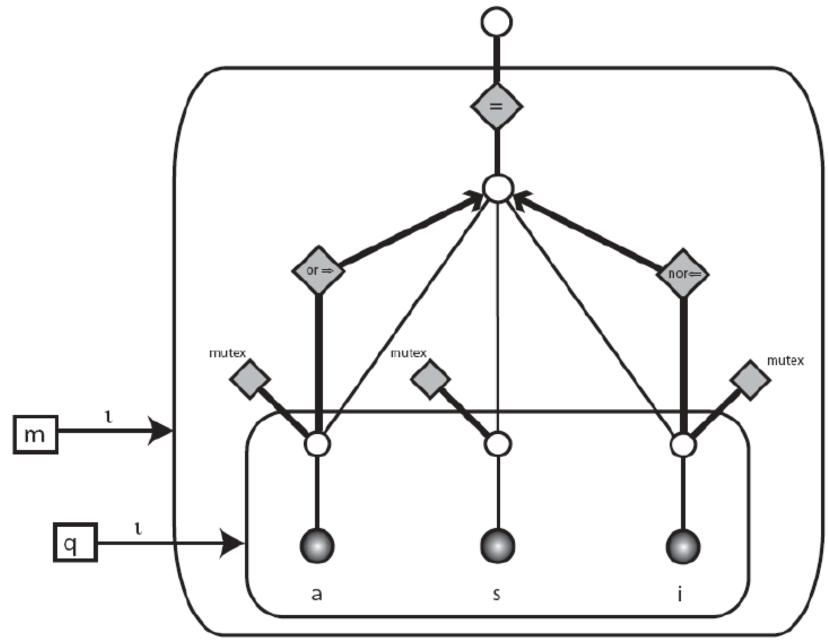


$$Y_f = \frac{\prod_q [(1+s_q)^{n-1} s_q (1+a_q)^n] + L \prod_q [(1+cs_q)^{n-1}(cs_q)(1+i_q)^n]}{\prod_q [(1+s_q)^n (1+a_q)^n] + L \prod_q [(1+cs_q)^n (1+i_q)^n]}$$

Derive from "partition function" Z = **generating function**

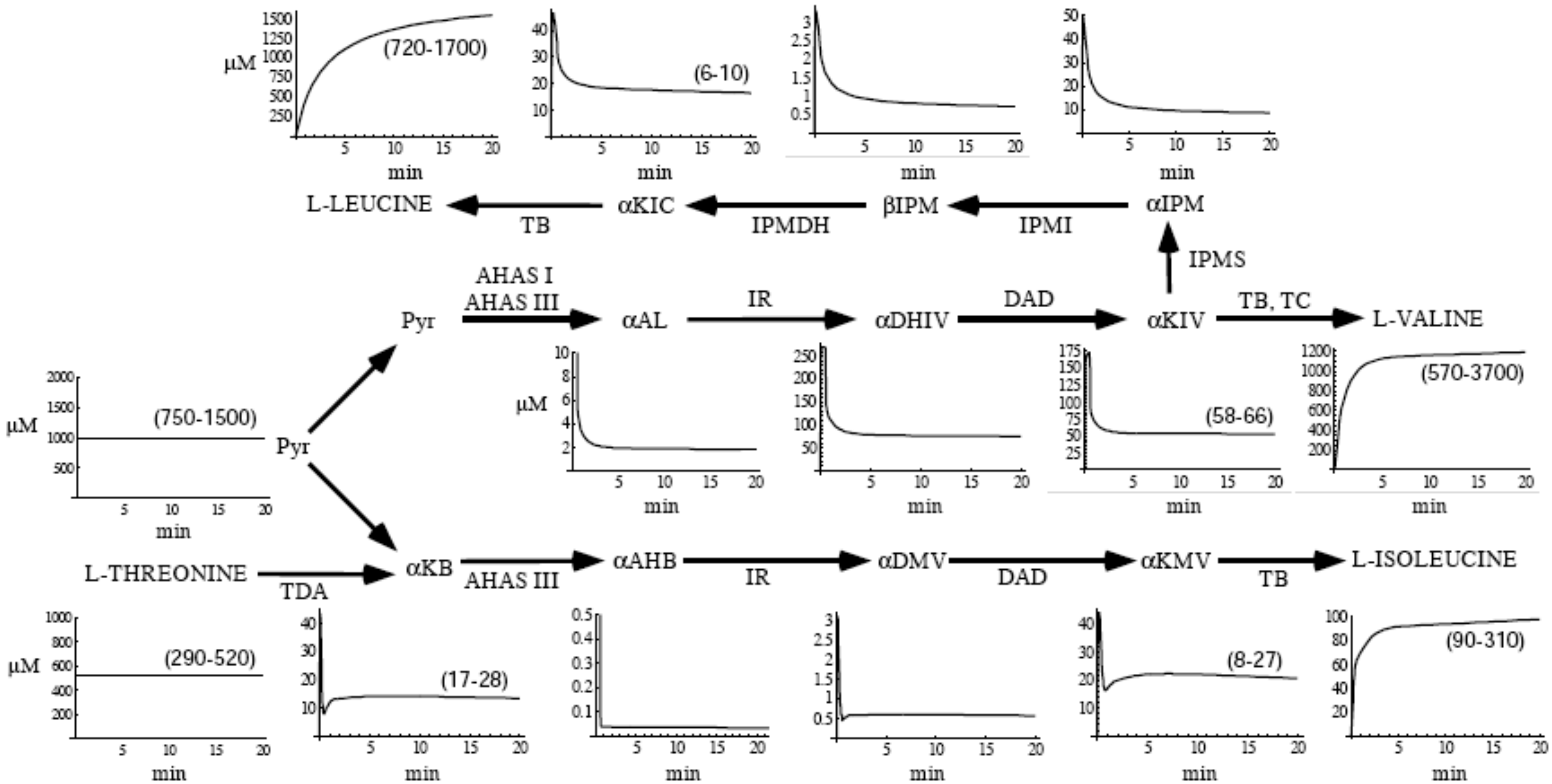
GMWC via EMCC





$$Y_f = \frac{\prod_q [(1+s_q)^{n-1} s_q (1+a_q)^n] + L \prod_q [(1+cs_q)^{n-1} (cs_q)(1+i_q)^n]}{\prod_q [(1+s_q)^n (1+a_q)^n] + L \prod_q [(1+cs_q)^n (1+i_q)^n]}$$

Biosynthesis of Valine, Leucine and Isoleucine

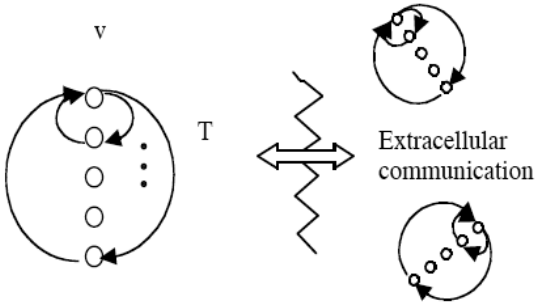


Yang et al., Journal of Biological Chemistry, 280(12):11224-32, Mar 25 2005

Transcriptional Gene Regulation Networks

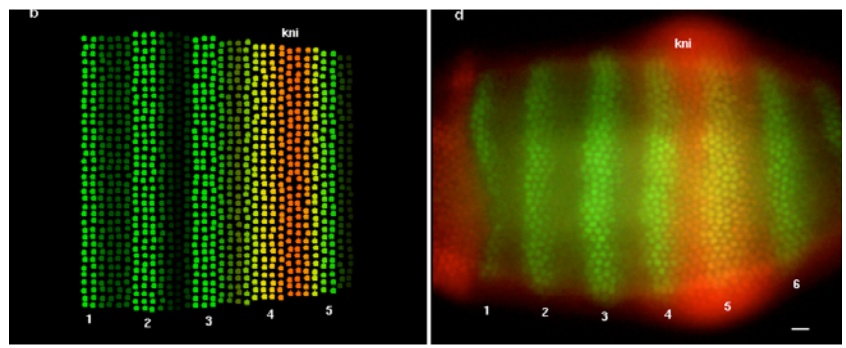
- Gene Regulation Network (GRN) model

E.g. *Drosophila* A-P axis:



$$\tau_i \dot{v}_i = g\left(\sum_j T_{ij} v_j + h_i\right) - \lambda_i v_i$$

[Mjolsness et al. J. Theor. Biol. 152: 429-453, 1991]

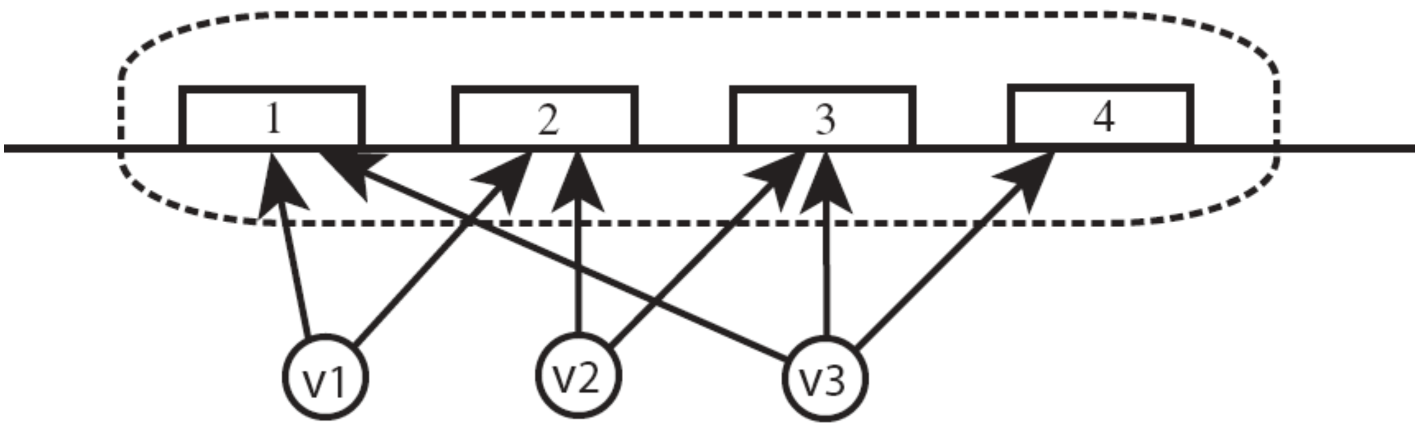


Drosophila *eve* stripe expression in model (right) and data (left). Green: *eve* expression, red: *kni* expression. From [Reinitz and Sharp, Mech. of Devel., 49:133-158, 1995]. Cf. [Jaeger et al 2004]

GRN ANN Equations 1991

Model statement and its derivation from stat mech:

[Mjolsness Sharp and Reinitz, J. Theor. Biol. 152: 429-453, 1991]



$$\boxed{\tau_i \dot{v}_i = g\left(\sum_j T_{ij} v_j + h_i\right) - \lambda_i v_i}$$

Model Reduction Example:

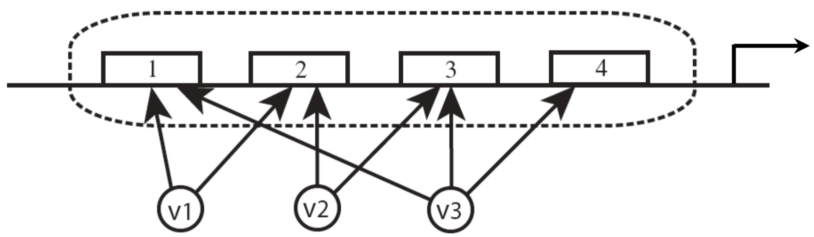
Gene Regulation Network Derived from Stat Mech

$$Z_{(0)}(z_{(0)}) = z_{(0)}\,\omega_{(0)} \prod_{b=1}^{B} \Xi^{+}_{(b)} + \prod_{b=1}^{B} \Xi^{-}_{(b)}$$

$$\Xi^{s}_{(b)} = 1 + \sum_{j=1}^{J} \omega^{s}_{(b\,j)}\, z_j + \sum_{j,k=1}^{J} \omega^{s}_{(b\,j\,k)}\, z_j\, z_k \quad \text{(including dimers)}$$

$$\text{Activation} = \left.\frac{\partial \log Z_0}{\partial \log z_{(0)}}\right|_{z_0=1}$$

$$= \frac{\omega_{(0)} \prod_{b=1}^{B} \Xi^{+}_{(b)}}{\omega_{(0)} \prod_{b=1}^{B} \Xi^{+}_{(b)} + \prod_{b=1}^{B} \Xi^{-}_{(b)}} = \sigma\left[\log\left(\omega_{(0)} \prod_{b=1}^{B} \Xi^{+}_{(b)} \Big/ \prod_{b=1}^{B} \Xi^{-}_{(b)}\right)\right]$$



$$\boxed{\text{Activation} \cong g\left(\sum_{j=1}^{J} T_{i\,j}\, v_j + \sum_{j,k=1}^{J} T_{i\,jk}\, v_j\, v_k + h_i\right)}$$

where

$$h_i = \log \omega_i = -\Delta G_i / k\,T \quad \text{and}$$
$$g(x) = 1/(1+\exp(-x))$$

$$\boxed{T_{(i\,j)} = \sum_{b=1}^{B} \omega^{+}_{(i\,b\,j)} - \sum_{b=1}^{B} \omega^{-}_{(i\,b\,j)} = \sum_{b=1}^{B} \exp(-\Delta G^{+}_{(i\,b\,j)}/k\,T) - \sum_{b=1}^{B} \exp(-\Delta G^{-}_{(i\,b\,j)}/k\,T)}$$

$$\tau_i \dot{v}_i = g\left(\sum_j T_{ij} v_j + h_i\right) - \lambda_i v_i$$

[J. Theor. Biol. 152: 429-453, 1991]

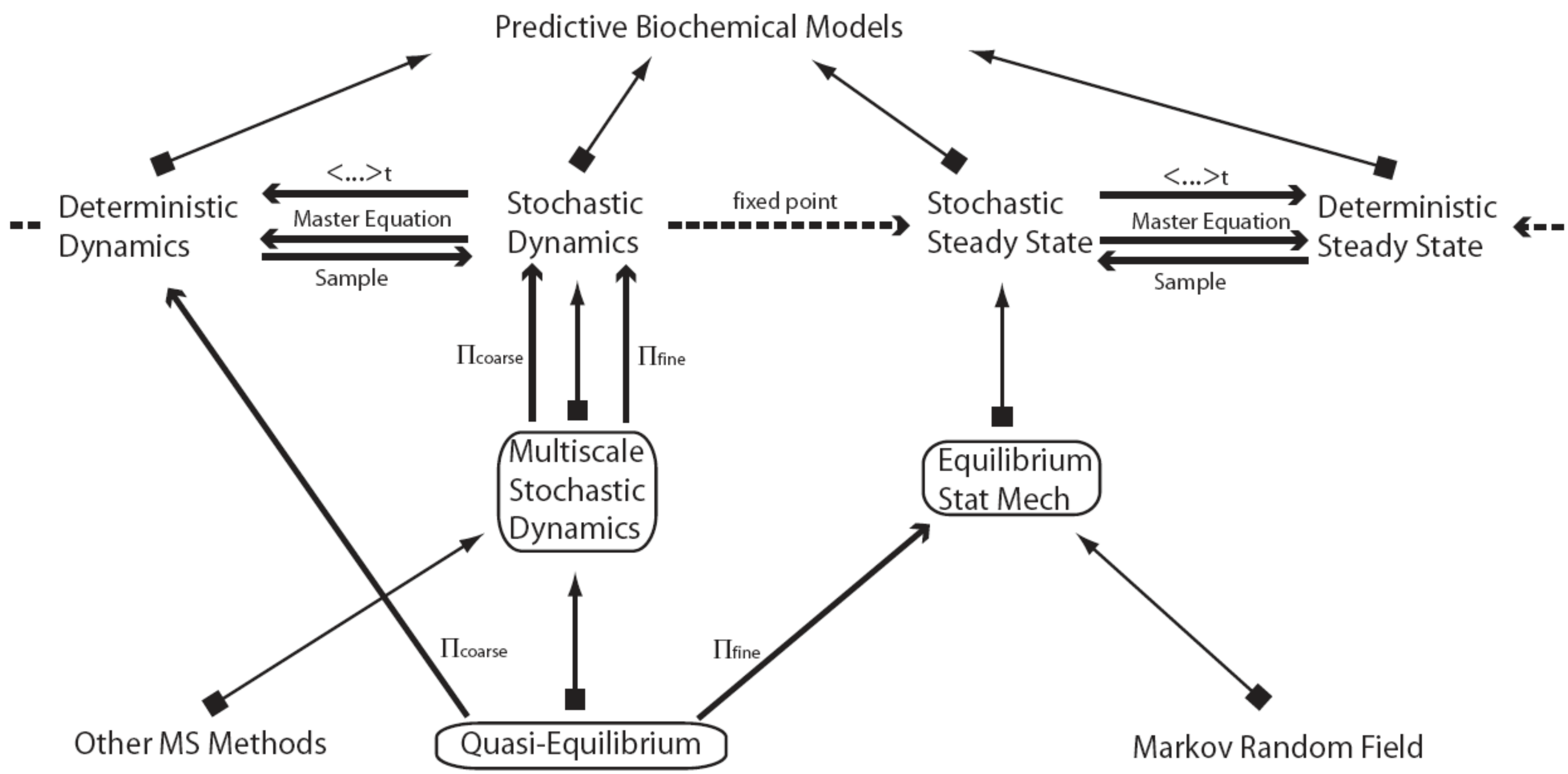
Conditions (newly relaxed):

$B \gg 1$, and
extreme (low or high) occupancy probability at each site
sites may now be heterogeneous

[J.Bioinformatics & Comp. Biology 5:2(b) 467-490, 2007]

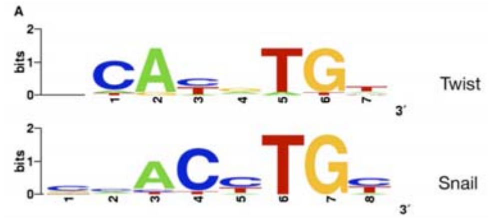
$\Rightarrow$ [MSR91] equations are no longer just "phenomenological".

Quasi-Equilibrium Models

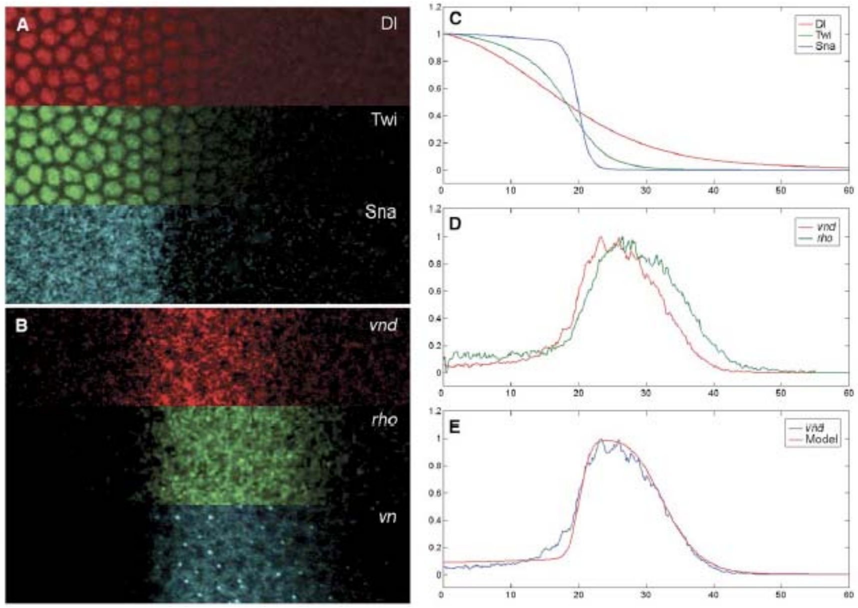


How to model transcriptional regulation?

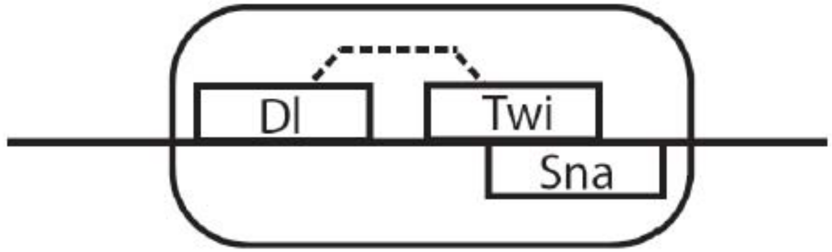
E.g. *Drosophila* D-V axis:



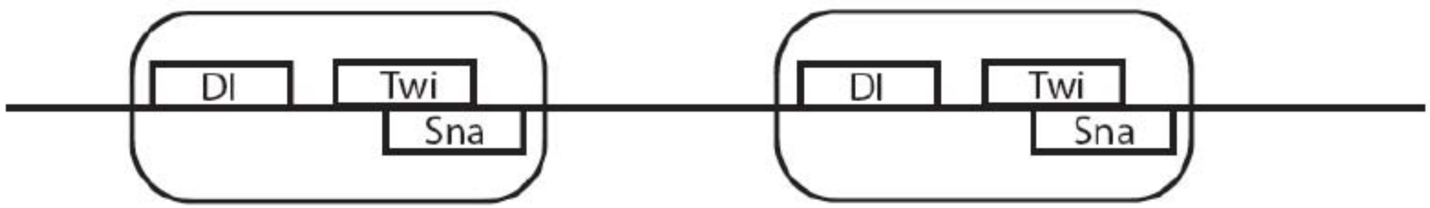
[Robert P. Zinzen, Kate Senger, Mike Levine, and Dmitri Papatsenko. Current Biology 16, 1–8, July 11, 2006]



DV axis promoter models



$$\frac{C_{Dl-Twi}K_{Dl}[Dl]K_{Twi}[Twi]}{1+K_{Twi}[Twi]+K_{Sna}[Sna]+K_{Dl}[Dl]+C_{Dl-Twi}K_{Dl}[Dl]K_{Twi}[Twi]+K_{Dl}[Dl]K_{Sna}[Sna]}$$



[Robert P. Zinzen, Kate Senger, Mike Levine, and Dmitri Papatsenko. Current Biology 16, 1-8, July 11 2006]

EMCC Recalculation

$$Z_{\text{composite},0} = Z_1^- Z_2^- + z_0 [Z_1^+ Z_2^- + Z_1^- Z_2^+ + Z_1^+ Z_2^+]$$

$$Z_1^+ = Z_2^+ = \sum_{\{(s_6, s_7, s_8) \mid s_6 \wedge s_7 \wedge \overline{s_7 \wedge s_8}\}} (\omega_{\text{Dl}} z_{\text{Dl}})^{s_6} (\omega_{\text{Twi}} z_{\text{Twi}})^{s_7} (\omega_{\text{Sna}} z_{\text{Sna}})^{s_8}$$

$$Z_1^+ = Z_2^+ = \omega_{\text{Dl}} z_{\text{Dl}} \omega_{\text{Twi}} z_{\text{Twi}}$$

$$Z_1^- = Z_2^- = \ldots$$

$$= 1 + \omega_{\text{Twi}} z_{\text{Twi}} + \omega_{\text{Dl}} z_{\text{Dl}} + \omega_{\text{Sna}} z_{\text{Sna}} + \omega_{\text{Dl}} z_{\text{Dl}} \omega_{\text{Sna}} z_{\text{Sna}}$$

Probability(at least one promoter is active) =

$$\frac{\partial \log Z_{\text{composite},0}}{\partial z_0}\bigg|_{z_0=1} = \frac{Z_1^+ Z_2^- + Z_1^- Z_2^+ + Z_1^+ Z_2^+}{Z_1^- Z_2^- + Z_1^+ Z_2^- + Z_1^- Z_2^+ + Z_1^+ Z_2^+}$$

$$\boxed{= 1 - \left(1 - \frac{Z_1^+}{Z_1^- + Z_1^+}\right)\left(1 - \frac{Z_2^+}{Z_2^- + Z_2^+}\right)}$$

Composition Theorem for Partition Functions

If

$$\boxed{Z_i\,(\boldsymbol{z}_i) = \sum_{\{\boldsymbol{s}_i \,|\, P_i\,(\boldsymbol{s}_i)\}} \left(\prod_a z_{i\,a}{}^{s_{i\,a}}\right) \prod_{\{\boldsymbol{\sigma}_i \,|\, Q_i\,(\boldsymbol{\sigma}_i)\}} (\omega)_{\boldsymbol{\rho}(\boldsymbol{\sigma}_i)}\,(\boldsymbol{s}_i) = \sum_{\{\boldsymbol{v}_i \,|\, \hat{P}_i(\boldsymbol{v}_i)\}} \left(\prod_{a \in V(i)} z_{i\,a}{}^{v_{i\,a}}\right) Z_i(\boldsymbol{v}_i,\, \boldsymbol{z}_i)}$$

is a set of partition functions, then the partition function for composite objects with root node i is:

$$Z_{\text{composite } i}\,(\boldsymbol{\zeta}_i,\, \{\boldsymbol{z}_j\}) = \sum_{\{\boldsymbol{v}_i \,|\, \hat{P}_i(\boldsymbol{v}_i)\}} \left(\prod_{a \in V(i)} z_{i\,a}{}^{v_{i\,a}}\right) Z_i\left(\boldsymbol{v}_i,\, \left\{\tilde{z}_{i\,b} \mapsto \varsigma_{i\,b}\, \tilde{Z}_{i\,\boldsymbol{v}_i\,b}\right\}\right)$$

$$\boxed{= \left[\sum_{\{\boldsymbol{v}_i \,|\, \hat{P}_i(\boldsymbol{v}_i)\}} \left(\prod_{a \in V(i)} z_{i\,a}{}^{v_{i\,a}}\right) Z_i(\boldsymbol{v}_i,\, \tilde{z}_{i\,\boldsymbol{v}_{ib}\,b})\right] \left(\tilde{z}_{i\,\boldsymbol{v}_{ib}\,b} \mapsto \varsigma_{i\,b}\, \tilde{Z}_{i\,\boldsymbol{v}_i\,b}\right)}$$

$$\tilde{Z}_{i\,\boldsymbol{v}_i\,b} = \tilde{Z}_{i\,\boldsymbol{v}_i\,b}\left(\left\{\tilde{z}_{i\,\boldsymbol{v}_i\,b\,j\,r} \mapsto Z_j(\boldsymbol{v}_j(\boldsymbol{v}_i),\, \boldsymbol{z}_j)\right\}\right)$$

where

$$\boxed{\begin{gathered} \tilde{Z}_{i\,\boldsymbol{v}_i\,b}(\{z_{i\,\boldsymbol{v}_i\,b\,j\,r}\}) = \\ \sum_{\left\{\tilde{s}_{i\,b\,j\,r} \in \{0,1\} \,\middle|\, \tilde{s}_{i\,b\,j\,r} \leq \Gamma_{i\,b\,\boldsymbol{v}_i,\,j\,r} \wedge \sum_{j,r} \tilde{s}_{i\,b\,j\,r} = 1\right\}} \left(\prod_{\{j\,r\}} (\tilde{z}_{i\,\boldsymbol{v}_i\,b\,j\,r})^{\tilde{s}_{i\,b\,j\,r}}\right) \left(\prod_{\left\{\sigma_{i\,a},\, \tilde{\sigma}_{i\,b\,j\,r} \,\middle|\, \tilde{Q}_{i\,b}(\{\sigma_{i\,a},\, \tilde{\sigma}_{i\,b\,j\,r} | i\,b\})\right\}} (\omega)_{\boldsymbol{\rho}(\boldsymbol{\sigma}_i,\, \tilde{\boldsymbol{\sigma}}_{i\,b})}\,(\boldsymbol{v}_i,\, \tilde{\boldsymbol{s}}_{i\,b})\right) \end{gathered}}$$

and

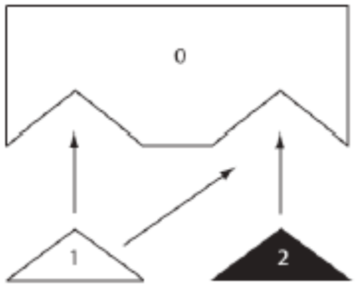
Grammar of possible binding relationships

$$\boldsymbol{v}_j(\boldsymbol{v}_i) = \sum_{\{\boldsymbol{v}_j\}} \boldsymbol{v}_j \prod_{a \in V(i)} \delta(v_{i\,a},\, v_{j\,a'})^{C_{(i\,b\,j\,r)(a\,a')}}$$

and

$\boldsymbol{v}_{i\,b}$ is the minimal subset of $\boldsymbol{v}_i$ components that interact with $\tilde{\boldsymbol{s}}_{i\,b}$ through $(\omega)_{\boldsymbol{\rho}(\boldsymbol{\sigma}_i,\, \hat{\boldsymbol{\sigma}}_{i\,b})}$.

EMCC examples



- Multiple binding sites

(c) Grammar: $\Gamma_{0111} = \Gamma_{0211} = \Gamma_{0221}\ \Gamma_{01\varnothing} = 1$; all others $=0$. $\hat{P}_{01} = (s_{0111} \leqslant 1)$ and all other $s_{0***} = 0$. $\hat{P}_{02} = (s_{0211} + s_{0221} \leqslant 1)$ and all other $s_{2***} = 0$. $P_0 = \mathrm{Mutex}(s_{0111}, s_{1121}) \wedge \mathrm{Mutex}(s_{0211}, s_{0221})$.

$$Z_0 = (1 + \omega_{11}\,\varsigma_1\,z_1)\,(1 + \omega_{21}\,\varsigma_2\,z_1 + \omega_{22}\,\varsigma_2\,z_2)$$

- Polymers

Grammar: $\Gamma_{1111} = 1$; all others $=0$. $\hat{P}_{01} = (s_{0111} \leqslant 1)$ and all other $s_{0***} = 0$. $P_0 = T$. $Z_1 = 1 + \omega_1\,\varsigma_1\,z_1$. Recursion means $z_1 = Z_1$, so

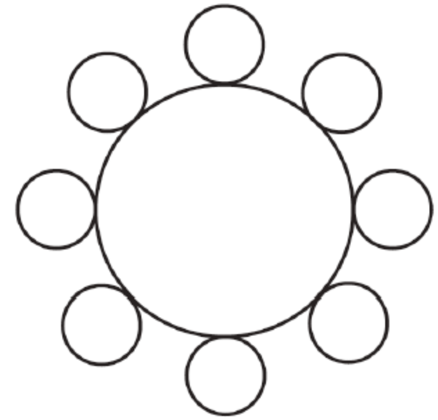
$$Z_1 = 1/(1 - \omega_1\,\varsigma_1) = \sum_{s=0}^{\infty} (\omega_1\,\varsigma_1)^s$$

- Dendrimers

$$Z_1(\varsigma_1, \varsigma_2) = (1 + \omega_1\,\varsigma_1\,Z_1(\varsigma_1, \varsigma_2))\,(1 + \omega_2\,\varsigma_2\,Z_1(\varsigma_1, \varsigma_2))$$

$$Z_1 = \frac{1 - \omega_1\,\varsigma_1 - \omega_2\,\varsigma_2 \pm \sqrt{(1 - \omega_1\,\varsigma_1 - \omega_2\,\varsigma_2)^2 - 4\,\omega_1\,\omega_2\,\varsigma_1\,\varsigma_2}}{\omega_1\,\omega_2\,\varsigma_1\,\varsigma_2}$$

Ring of Rings



$$Z_0(z) = \frac{{y_1}^{-N_1/2}}{2^{N_1}} \left(\left(z\, {y_1}^2 + 1 + \sqrt{z^2\, {y_1}^4 + 4\, z\, {y_1}^4 + 1} \right)^{N_1} + \left(z\, {y_1}^2 + 1 - \sqrt{z^2\, {y_1}^4 + 4\, z\, {y_1}^4 + 1} \right)^{N_1} \right)$$

All square roots cancel for integer values of N_1 .

As $N_1, N_2 \to \infty$,

$$Z_0(Z_1(z)) \to 2^{-N_1}\, y_1^{-\frac{N_1}{2}}$$

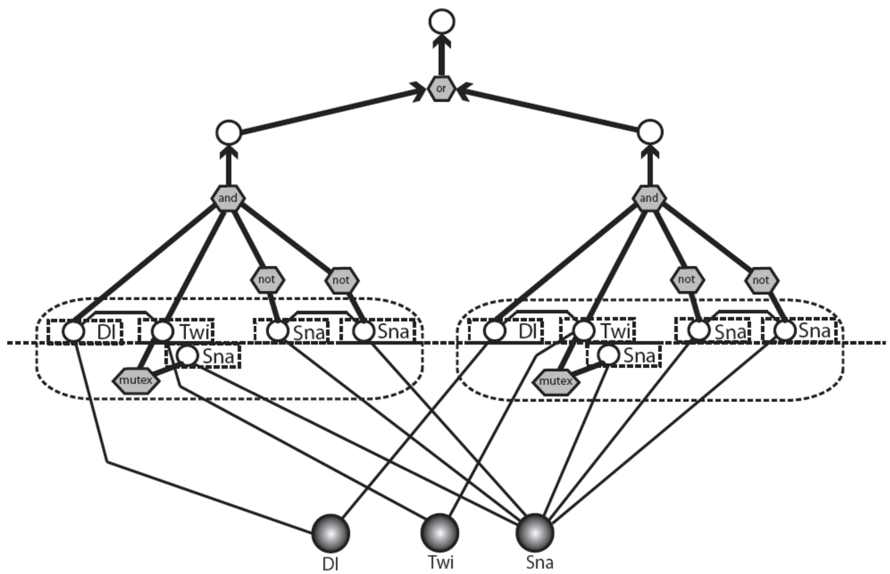
$$\left(1 + 2^{-N_2}\, y_1^2\, y_2^{-\frac{N_2}{2}} \left(1 + z\, y_2^2 + \sqrt{1 + z\,(4+z)\, y_2^4} \right)^{N_2} + \sqrt{\left(1 + 8^{-N_2}\, y_1^4\, y_2^{-N_2} \left(1 + z\, y_2^2 + \sqrt{1 + z\,(4+z)\, y_2^4} \right)^{N_2} \right.} \right.$$

$$\left. \left. \left(4^{1+N_2}\, y_2^{\frac{N_2}{2}} + 2^{N_2} \left(1 + z\, y_2^2 + \sqrt{1 + z\,(4+z)\, y_2^4} \right)^{N_2} \right) \right) \right)^{N_1}$$

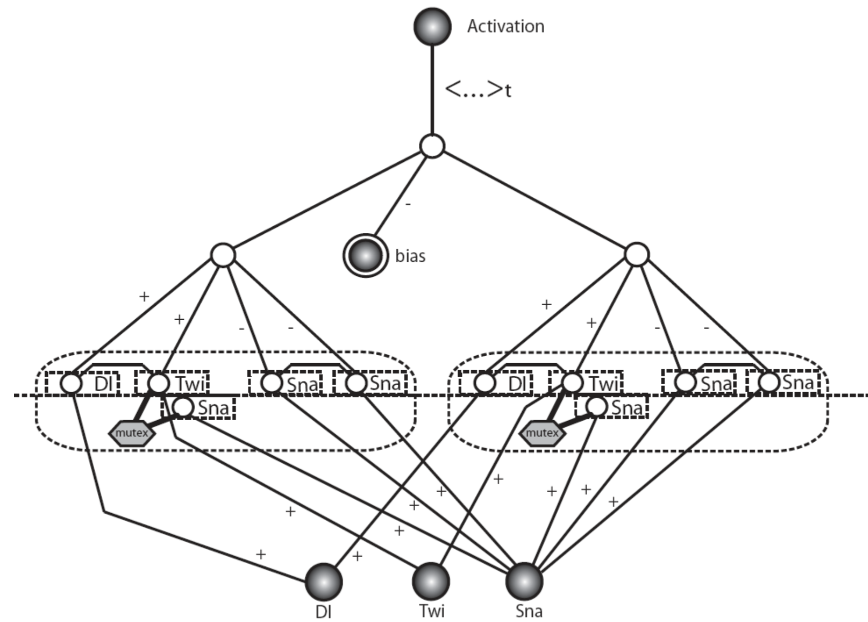
... a formula in which, for finite integer N's, all square roots must cancel out.

There is a longer formula, exact for all sizes.

Hard vs. Soft Logic



Zinzen et al. modification



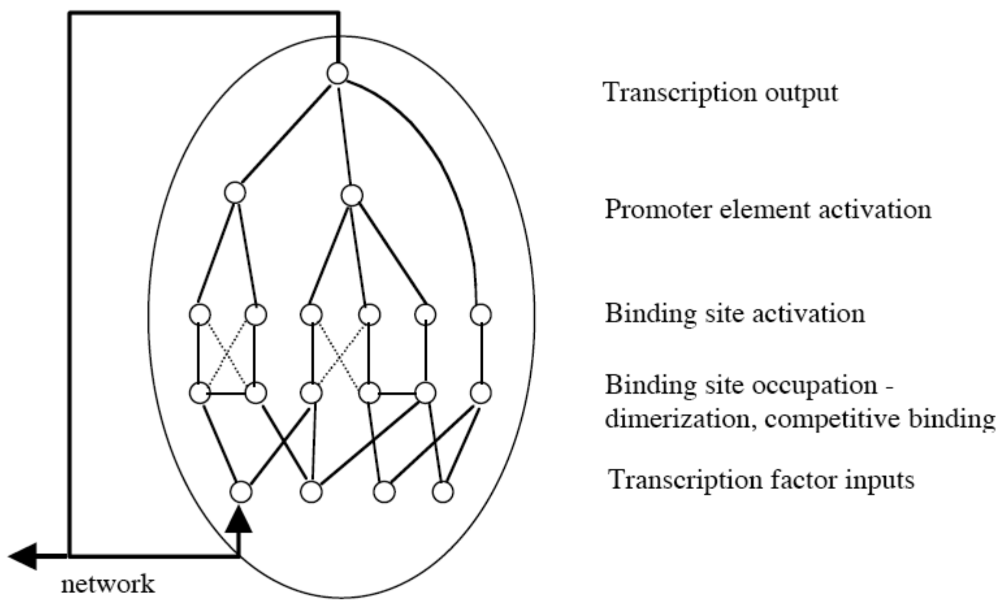
Hierarchical Cooperative Activation (HCA)

Modeling Eucaryotic Transcription Complexes: Hierarchical Cooperative Activation (HCA) Model

$$\tau_i \frac{dv_i}{dt} = [transcribing]_i - \lambda_i v_i$$

$$[transcribing]_i = g(u_i) = \frac{Ju_i}{1+Ju_i}$$

$$u_i = \prod_{\alpha \in i}\left(\frac{1+J_\alpha P_\alpha}{1+\hat{J}_\alpha P_\alpha}\right)$$



$$P_\alpha = g_\alpha(\tilde{u}_\alpha) = \frac{\tilde{K}_\alpha \tilde{u}_\alpha}{1+\tilde{K}_\alpha \tilde{u}_\alpha}$$

$$\tilde{u}_\alpha = \prod_{b \in \alpha}\left(\frac{1+K_b v_{j(b)}^{n(b)}}{1+\hat{K}_b v_{j(b)}^{n(b)}}\right)$$

$$f_{\alpha b} = \frac{K_b v_{j(b)}^{n(b)}}{1+K_b v_{j(b)}^{n(b)}} \qquad \hat{f}_{\alpha b} = \frac{\hat{K}_b v_{j(b)}^{n(b)}}{1+\hat{K}_b v_{j(b)}^{n(b)}}$$

In: Computational Methods in Molecular Biology, eds. J. M. Bower and H. Bolouri, MIT Press 2001

HCA$^-$ Z and ANN-like Equations

- Assume many binding sites per module
- Assume extreme (usually low) occupancy per site

$$Z_{(0)}(\tilde{z}, \zeta_{(2\ m)} = 1) = z_{(0)}\ \omega_{(0)} \prod_{m=1}^{M}\left[\omega_{(2\ m)}^{++} \prod_{b=1}^{B(m)} \Xi_{(m\ b)}^{++} + \prod_{b=1}^{B(m)} \Xi_{(m\ b)}^{--}\right] + \prod_{m=1}^{M}\left[\omega_{(2\ m)}^{-+} \prod_{b=1}^{B(m)} \Xi_{(m\ b)}^{-+} + \prod_{b=1}^{B(m)} \Xi_{(m\ b)}^{+-}\right]$$

$$\Xi_{(m\ b)}^{s\ s'} = 1 + \sum_{j=1}^{J} \omega_{(m\ b\ j)}^{s\ s'}\ z_j + \sum_{j=1}^{J} \omega_{(m\ \sigma(b)\ j)}^{s\ s'}\ z_j + \sum_{j,\,k=1}^{J} \omega_{(m\ b\ j\ k)}^{s\ s'}\ z_j\ z_k + \sum_{j,\,k=1}^{J} \omega_{(m\ \sigma(b)\ j\ k)}^{s\ s'}\ z_j\ z_k$$

$$\boxed{\begin{aligned} \text{Activation} &\cong g\left(h_{(0)} + M + \sum_{m=1}^{M}\left(h_{(m)}^{+} - h_{(m)}^{-} - 1\right) v_{(m)}\right), \\ v_{(m)} &= g\left(h_{(m)}^{-} + \sum_{j=1}^{J} T_{(m\ j)}\ z_j + \sum_{j,\,k=1}^{J} T_{(m\ j\ k)}\ z_j\ z_k\right) \end{aligned}}$$

where $g(x) = 1/(1+\exp(-x))$

$$T_{(m\ j)} = T_{(m\ j)}^{+} - T_{(m\ j)}^{-} \text{ and } T_{(m\ j\ k)} = T_{(m\ j\ k)}^{+} - T_{(m\ j\ k)}^{-}$$

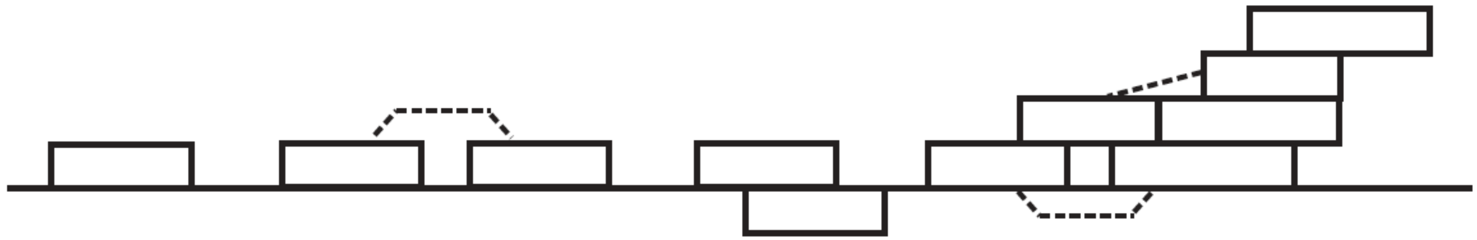
$$T_{(m\ j)}^{\pm} = \sum_{b=1}^{B(m)} \omega_{(m\ b\ j)}^{\pm} = \sum_{b=1}^{B(m)} \exp\left(-\Delta\ G_{(m\ b\ j)}^{\pm} / k\ T\right),$$

$$T_{(m\ j\ k)}^{\pm} = \sum_{b=1}^{B(m)} \omega_{(m\ b\ j\ k)}^{\pm} = \sum_{b=1}^{B(m)} \exp\left(-\Delta\ G_{(m\ b\ j\ k)}^{\pm} / k\ T\right), \text{ and}$$

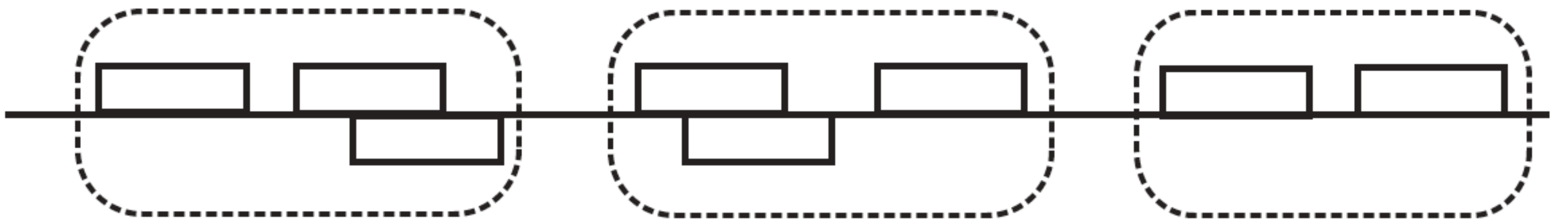
$$h_{(m)}^{+} = \log \omega_{(m)}^{+} = -\Delta\ G_{(m)} / k\ T$$

$$h_{(0)} = \log \omega_{(0)} = -\Delta\ G_{(0)} / k\ T$$

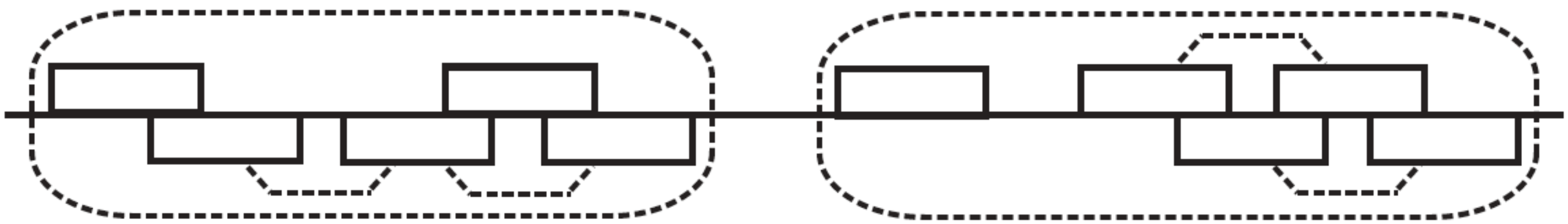
Modeling challenges



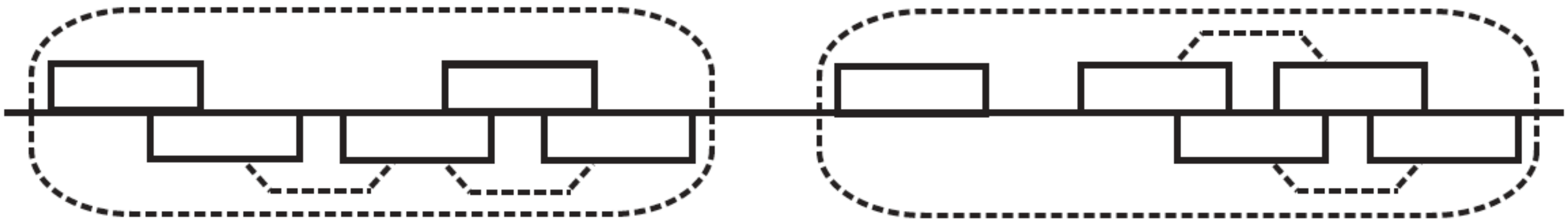
- Simplify to Hierarchical Cooperative Activation (HCA [2001]):



- … or to HCA+ [BGRS 2006]:



HCA$^+$



Transfer matrix method for max site overlap = 2:

$$Z = (1\ 1\ 1) \cdot \left\{ \prod_{i=k \searrow 1} \begin{pmatrix} 1 & 1 & 1 \\ z_{2\,i+1} & z_{2\,i+1}\ \omega_{2\,i-1,\,2\,i+1} & 0 \\ z_{2\,i+2} & z_{2\,i+2} & z_{2\,i+2}\ \omega_{2\,i,\,2\,i+2} \end{pmatrix} \right\} \cdot \begin{pmatrix} 1 \\ z_1 \\ z_2 \end{pmatrix}$$

Calculation is polynomial in # of binding sites per module.

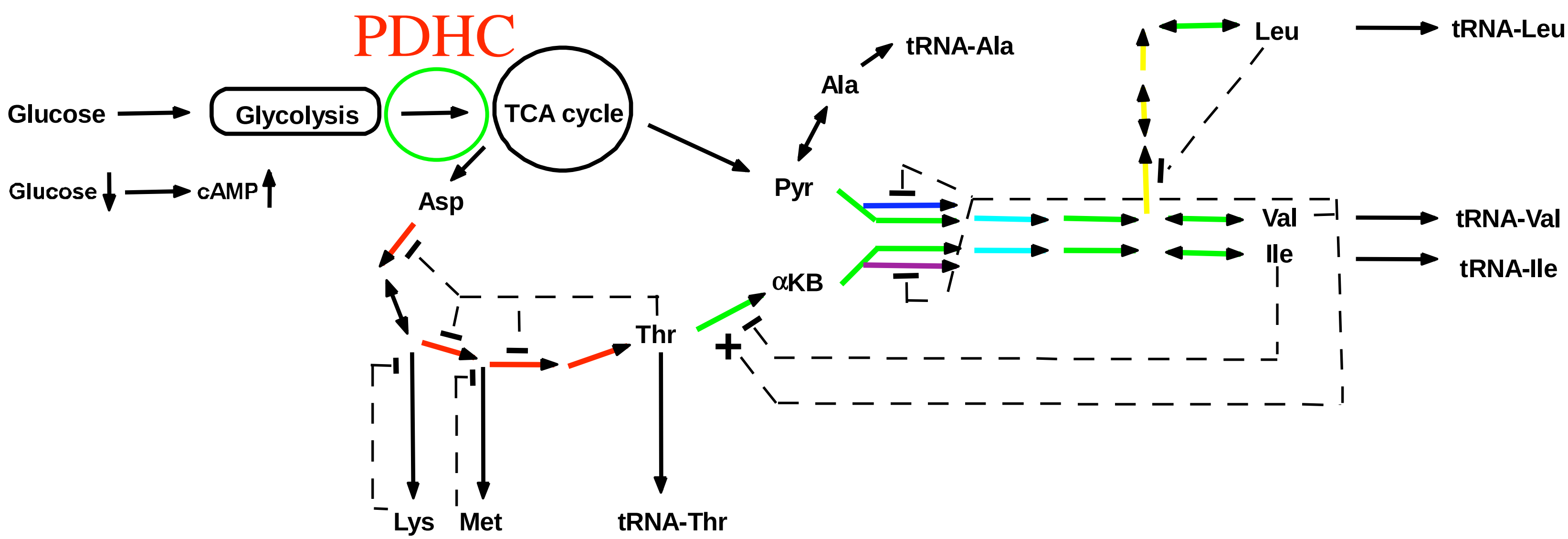
Transfer matrix method still works for higher stacks:

Max overlap+1 (= matrix dimension) is bounded by width of the sites. Tree module structure still OK.

Methods

- Partition function algebra
- Composition principle (EMCC)
- Random Steady State (RSS) model

Amino Acid Syntheses



Kmech and (Val, Leu, Ile) biosynthesis:

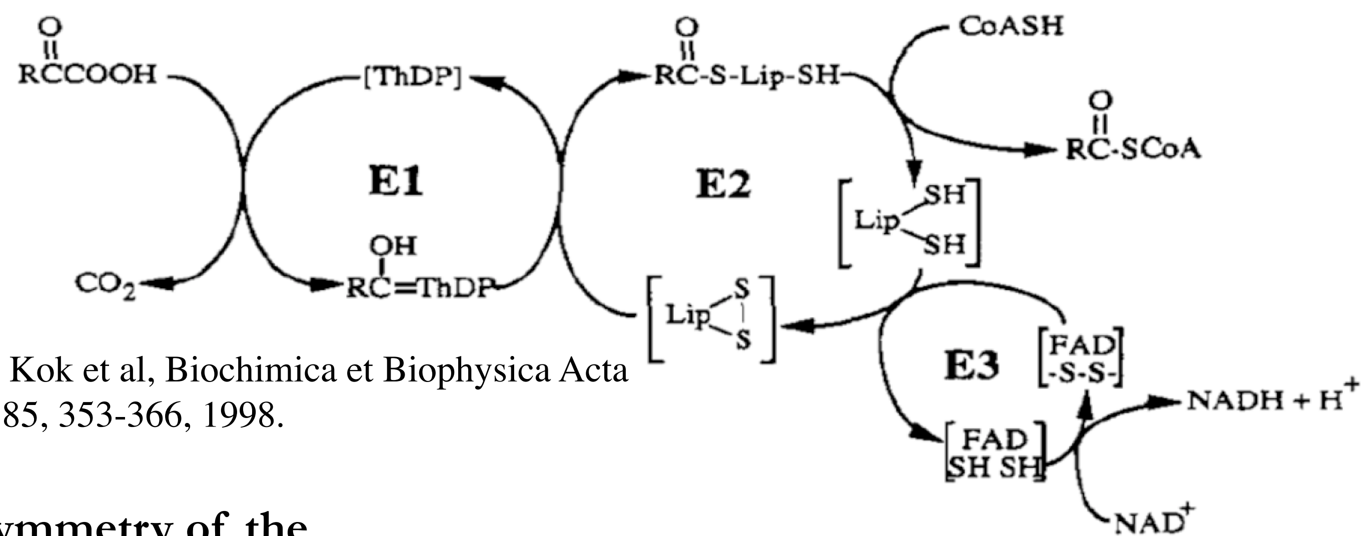
[Yang, Shapiro, Hung, Mjolsness, and Hatfield, *Journal of Biological Chemistry*, 280(12):11224-32, 2005]

[Yang, Shapiro, Hung, Mjolsness *Bioinformatics* 21: 774-780, 2005.]

Thr biosynthesis from Asp:

[Najdi, Shapiro, Hatfield, and Mjolsness, *Journal of Bioinformatics and Computational Biology*, 4:335-355, 2006.]

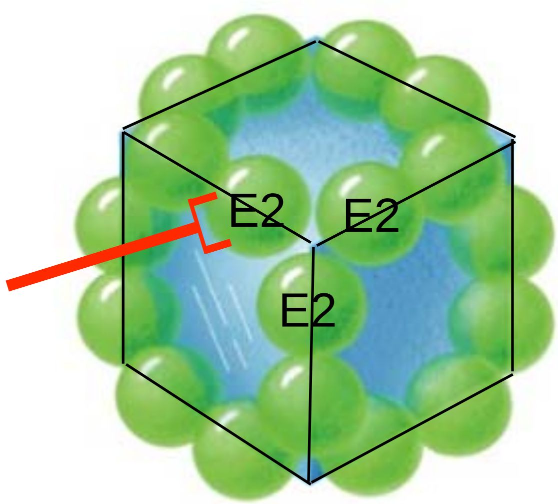
Enzyme complex structure (PDH and KGDH)



de Kok et al, Biochimica et Biophysica Acta 1385, 353-366, 1998.

Cubic symmetry of the E2 core

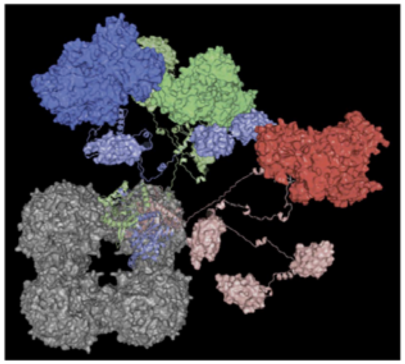
E1 or E3



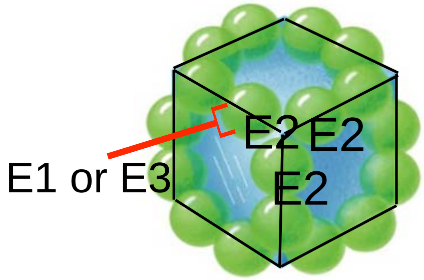
- 24 E2: 8 trimers
- E1 and E3: 24 dimers (optimally 2 E1 : 1 E3)

PDHC E2 structure

- Lipoyl domain "arm(s)" each sustain full reaction
  - [de Kok et al, Biochimica et Biophysica Acta 1385, 353-366, 1998.]
- E1/E3 binding domain "tethered" to rest of E2
  - Tether length ~ 11nm
  - [Murphy and Jensen, Structure 13, 1765-73, Dec 2005.]
  - Ideal ratio of 2:1 not guaranteed

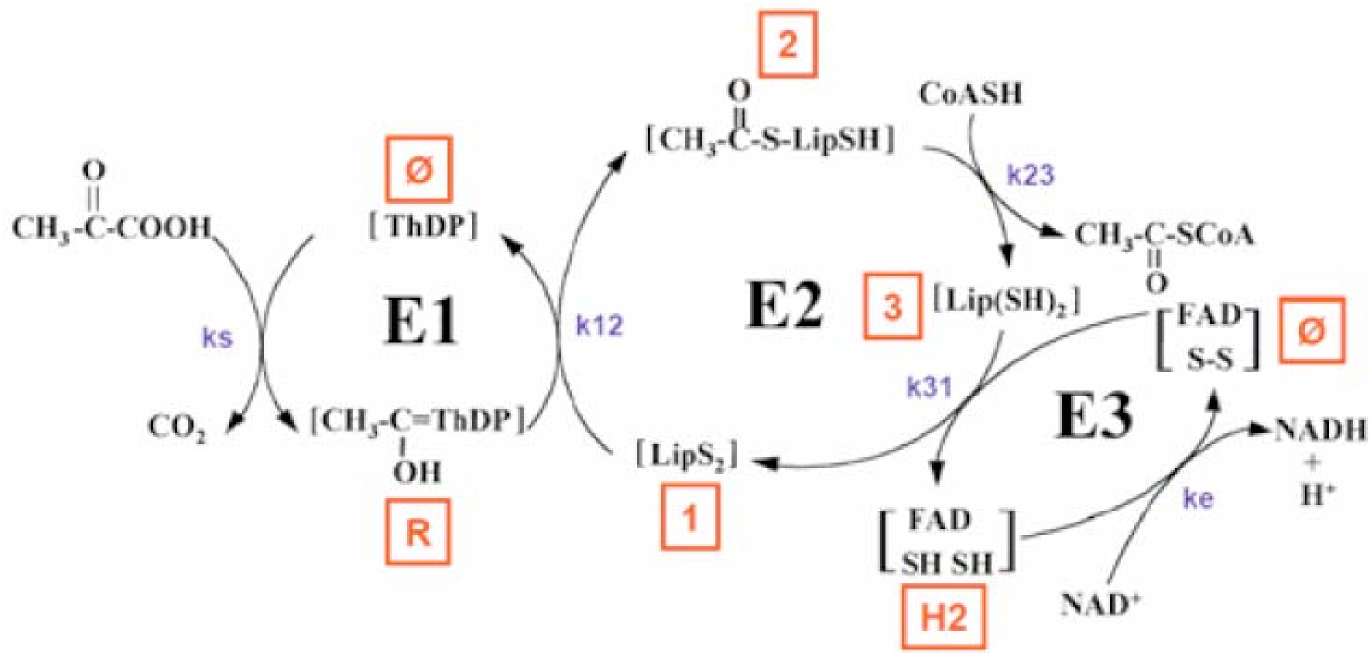


- E2's in complex.
  - 3 E2's (1 trimer) per vertex.
  - cube, dodecahedron, isolated trimer structures known in different species.

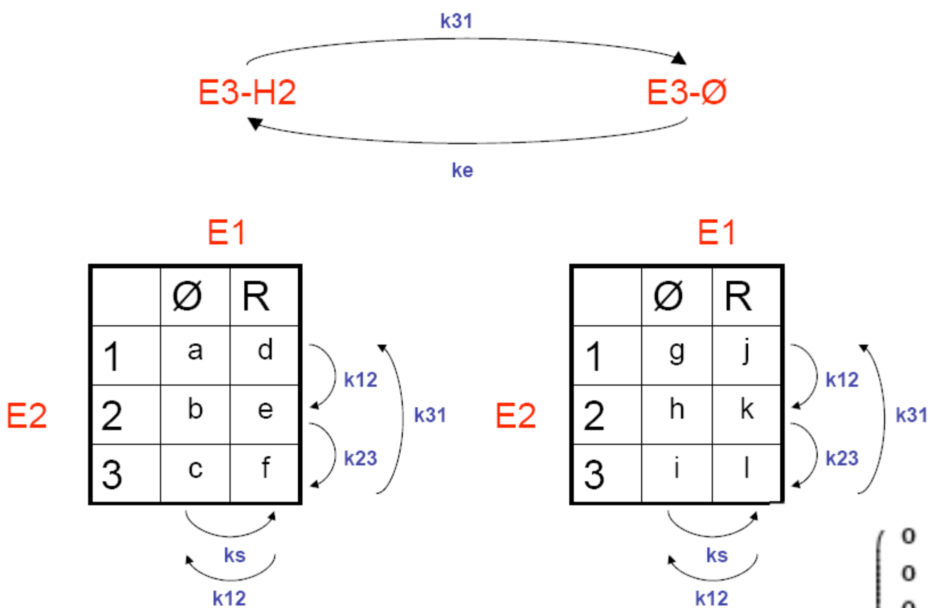


Steady State Model

- Pyruvate dehydrogenase reactions



State transitions in 12 dimensions



$$
\mathrm{Hhat} = \begin{pmatrix}
0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & k31 & 0 & 0 & 0 \\
0 & 0 & 0 & k12 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
0 & k23 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
ks & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & k31 \\
0 & ks & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
0 & 0 & ks & 0 & k23 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
ke & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
0 & ke & 0 & 0 & 0 & 0 & 0 & 0 & 0 & k12 & 0 & 0 \\
0 & 0 & ke & 0 & 0 & 0 & 0 & k23 & 0 & 0 & 0 & 0 \\
0 & 0 & 0 & ke & 0 & 0 & ks & 0 & 0 & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & ke & 0 & 0 & ks & 0 & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & 0 & ke & 0 & 0 & ks & 0 & k23 & 0
\end{pmatrix}
$$

Resulting rate law

```
FullSimplify[Series[
  rate3 /. {ks → (k s1)/(km + s1), k12 → ϵ n1 k, k23 → (k s2)/(km + s2), k31 → k (3 - n1), ke → k (3 - n1) / Sf},
  {Sf, 0, 3}]]
```

```
(k (-3 + n1) n1 s1 (km (-3 + n1) + (-4 + n1) s1) s2 (2 s1 s2 + km (s1 + s2)) ϵ) /
  ((-3 + n1) s1 (km (-3 + n1) + (-4 + n1) s1) s2 (2 s1 s2 + km (s1 + s2)) +
    n1 ((41 + n1 (-22 + 3 n1)) s1^3 s2^2 + km s1^2 s2 ((-4 + n1) (-10 + 3 n1) s1 + (67 - 40 n1 + 6 n1^2) s2) +
       km^3 (-3 + n1)^2 (s1^2 + s1 s2 + s2^2) +
       km^2 (-3 + n1) s1 ((-4 + n1) s1^2 + 2 (-7 + 2 n1) s1 s2 + (-13 + 4 n1) s2^2)) ϵ) -
 (k n1^3 s1^4 s2^3 (2 s1 s2 + km (s1 + s2)) (km^2 (-3 + n1) + (-5 + n1) s1 s2 + km (-4 + n1) (s1 + s2)) ϵ^3
    Sf^3) / ((-3 + n1) (km + s2) ((-3 + n1) s1 (km (-3 + n1) + (-4 + n1) s1) s2 (2 s1 s2 + km (s1 + s2)) +
       n1 ((41 + n1 (-22 + 3 n1)) s1^3 s2^2 + km s1^2 s2
             ((-4 + n1) (-10 + 3 n1) s1 + (67 - 40 n1 + 6 n1^2) s2) + km^3 (-3 + n1)^2 (s1^2 + s1 s2 + s2^2) +
          km^2 (-3 + n1) s1 ((-4 + n1) s1^2 + 2 (-7 + 2 n1) s1 s2 + (-13 + 4 n1) s2^2)) ϵ)^2) + O[Sf]^4
```

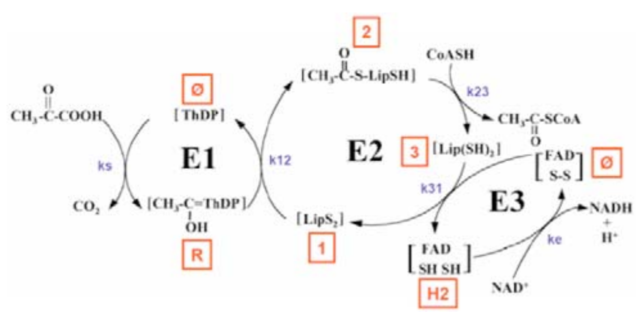
`rate[n1_, s1_, s2_, k_, km_, ϵ_]` = leading term in k31/ke

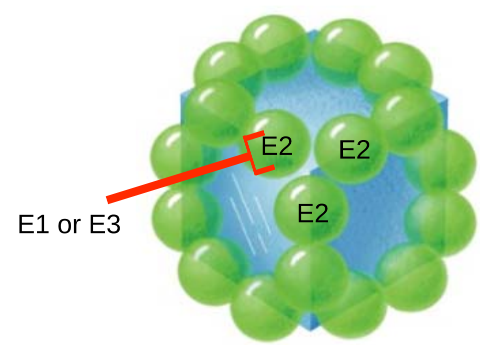
Random Steady State (RSS) model

Random Steady State (RSS) model
Case: isolated trimer

The reaction rate was derived by solving a 12x12 steady state system of the cycle of enzyme-catalyzed reactions

Random binding of E1 and E3 to E2 core modeled by a binomial distribution of accessible E1s and E3s





Result: *Equilibrium* at slow time scale;
Steady-state at fast time scale.
Different from quasi-equilibrium models

$$\sum_{n1=0}^{3} \text{Binomial}[3, n1]\, q^{n1} (1-q)^{3-n1} * \text{RATE}$$

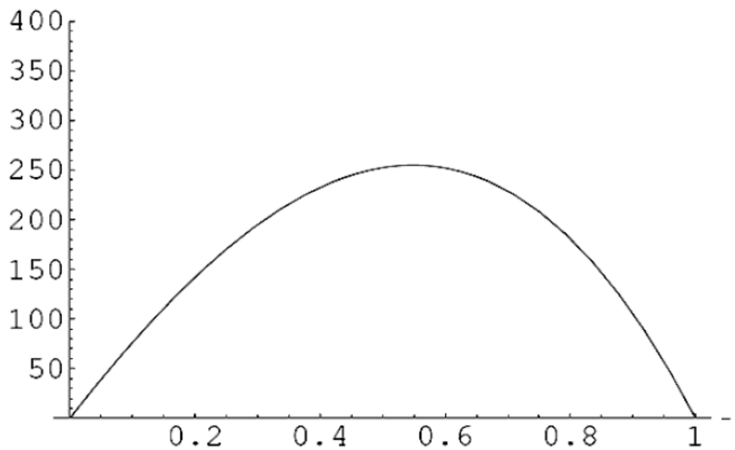
$$q = \frac{[E1]\,K1}{[E1]\,K1 + [E3]\,K3}$$

A minor tragedy:
Random E1/E3 occupancy => achievable rate << optimal rate

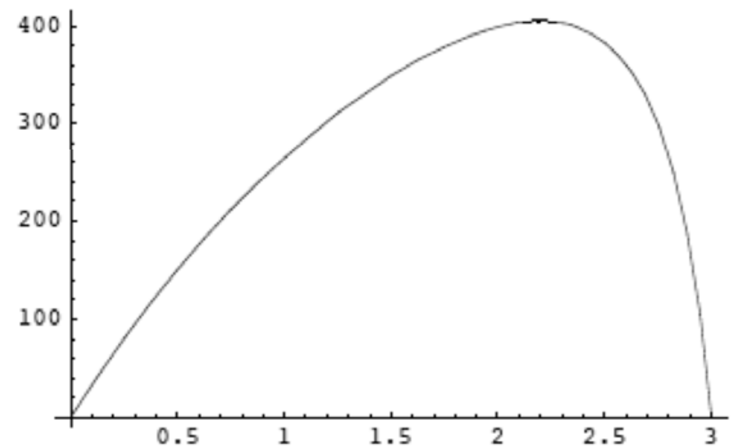
```
Plot[(Sum[Binomial[3, n1] q^n1 (1 - q)^(3 - n1) rate[n1, 10000, 10000, 2300, 1300, 0.15], {n1, 0, 3}]),
  {q, 0, 1}];
```

$$\sum_{n1=0}^{3}$$

```
Plot[rate[n1, 10000, 10000, 2300, 1300, 0.15], {n1, 0, 3}];
```

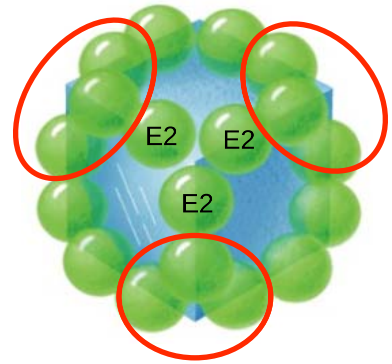


$$q = \frac{[E1]\,K1}{[E1]\,K1 + [E3]\,K3}$$



n_1

Hypothesis: Neighboring Vertex E2 Trimers Share E1/E3s



- Minimize chances of $n_1=0$ or 3 => no production.
- Structural tether models don't rule out sharing of E1/E3 capacity among trimers.
- Could explain the multi-trimer complex structure.
- Model with RSS
  - Requires more partition function technique
- Compare throughputs with isolated vertex hypothesis, and reported experiments

How to model shared, tethered E1/E3 sites?

- *Approximate* $Rate(n_1)$ with a low-degree polynomial, constraining *Rate(0)=Rate(3)=0.*
- *Replicate* n_1, $n_3=3-n_1$ by # of vertices: $n_{1,vertex}$
  - (optional) simplify to vertex + 3 neighbors
- Approximate multi-vertex partition function:

$$Z_{complex} = \prod_v Z(n_{1,v}, n_{3,v})$$

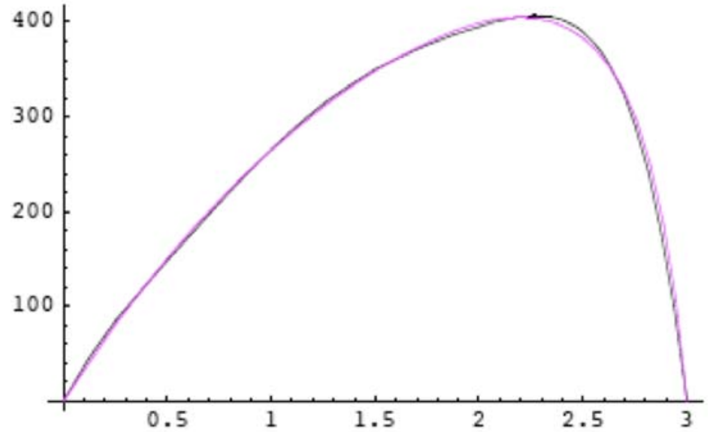
- Introduce *sharing* fraction $\alpha \in [0,1]$
- Evaluate: $Rate[(1-\alpha)n_{1,v} + \frac{\alpha}{|nbrs(v)|}\sum_{w \in nbrs(v)} n_{1,w}]$

Approximating *Rate(n_1)*

```
numsol = FindMinimum[error[λ, 5], Table[{λ[[i]], 1/pmax}, {i, 1, pmax}] /. pmax → 5]
```

$$\text{Plot}\left[\left\{\left(\boxed{(1 - n1/3)\sum_{p=1}^{5}\lambda_{[p]}\ ((p+1)\hat{\ }(p+1)/p\hat{\ }p)\ (n1/3)\hat{\ }p}\right) /.\ \text{numsol}[[2]],\right.\right.$$

```
  rate[n1, 10000, 10000, 2300, 1300, 0.15]}, {n1, 0, 3},
  PlotStyle → {CMYKColor[0, 0, 0, 1], CMYKColor[0, 1, 0, 0]}];
```



$$\boxed{\begin{aligned} ff[n\_] := \left(1 - \frac{n}{3}\right) (&428.0733339579392\grave{}\ n - 379.4019173077035\grave{}\ n^2 + \\ &632.2906157703737\grave{}\ n^3 - 364.17334380810087\grave{}\ n^4 + 81.76686063645717\grave{}\ n^5) \end{aligned}}$$

Technical points

(because we haven't had any yet)

- Each monomial in $\{n_{1,vertex}\}$ averages separately, by linearity of averaging.
- Each factor $(n_{1,vertex})^k$ averages separately at its own vertex, by independence of the vertices.
- So globally averaging polynomials in $n_{1,v}$ is *multilinear*.

```
rules = Flatten@Table[{m0^p -> ⟨n1^p⟩, m1^p -> ⟨n1^p⟩, m2^p -> ⟨n1^p⟩, m3^p -> ⟨n1^p⟩}, {p, 6, 1, -1}];
answer[q_, α_] = Expand[ff[(1 - α) m0 + α (m1 + m2 + m3) / 3]] /. rules;
```

Technical points

- Polynomial vector space bases: $(n_{1,v})^k$ vs. $(n_{1,v})_{(k)}$
- Vertex averages of $(n_{1,v})^k$ are related to those of $(n_{1,v})_{(k)} \equiv n_{1,v}!/(n_{1,v}-k)!$ by Stirling numbers, since

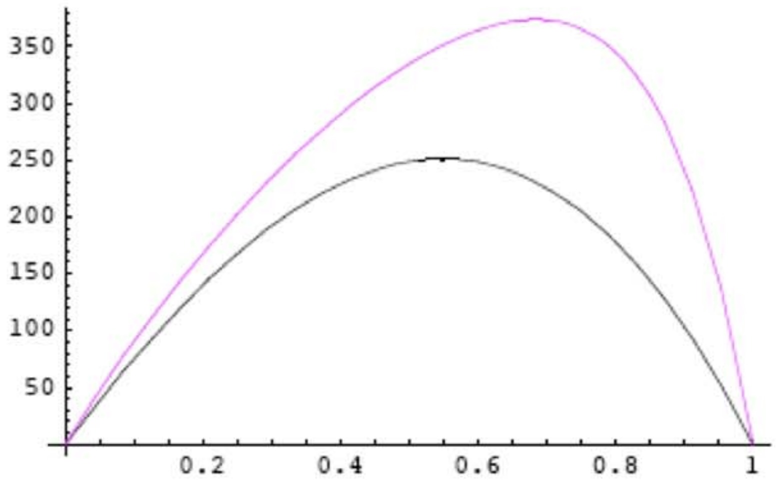
$$n^k = \sum_{l=0}^{k} \left\{ \begin{matrix} k \\ l \end{matrix} \right\} n_{(l)} \quad \text{and} \quad n_{(l)} = \sum_{m=0}^{l} \left[\begin{matrix} l \\ m \end{matrix} \right] n^m$$

- Averages of $(n_{1,vertex})_{(k)}$ are easy k^{th} derivatives of the vertex partition function. For a trimer, only *k=1,2,3* are nonzero.
- Then vertex averages $\langle n^k \rangle$ can be computed by recurrence, using

$$\langle n^k \rangle = \langle n_{(k)} \rangle - \sum_{l=0}^{k-1} \left[\begin{matrix} k \\ l \end{matrix} \right] \langle n^l \rangle$$

Resulting throughput gain

```
(* Comparison of sharing to no sharing *)

Plot[{∑_{n1=0}^{3} Binomial[3, n1] q^n1 (1 - q) ^ (3 - n1) rate[n1, 10000, 10000, 2300, 1300, 0.15],
  answer[q, 0.75]}, {q, 0, 1}, PlotStyle → {CMYKColor[0, 0, 0, 1], CMYKColor[0, 1, 0, 0]}];
```

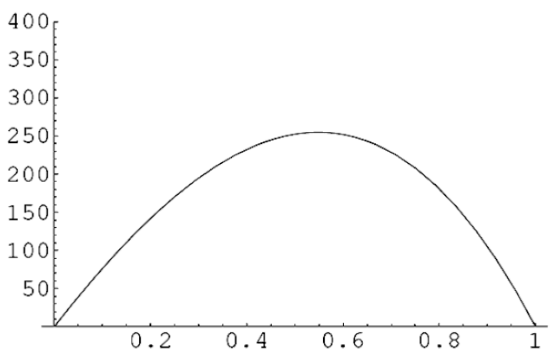



```
Maximize[answer[q, α], {q, α}]

{374.279, {q → 0.683579, α → 0.75}}
```

Satisficing solution:

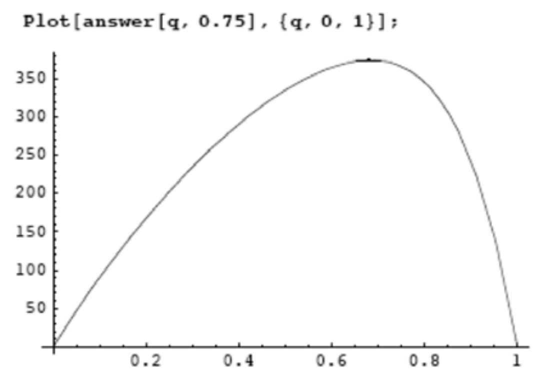
Shared random E1/E3 occupancy: achievable rate ~ optimal rate

No sharing (RSS)



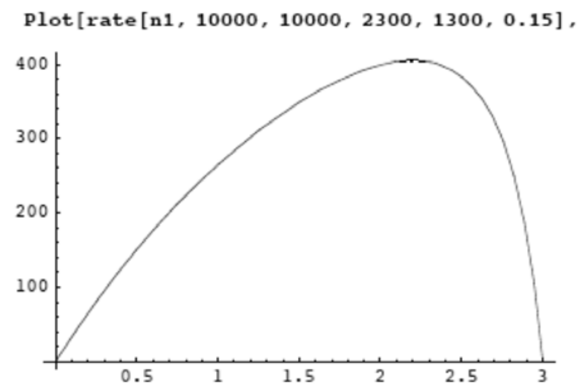
$$q = \frac{[E1]\,K1}{[E1]\,K1 + [E3]\,K3}$$

With sharing (RSS)



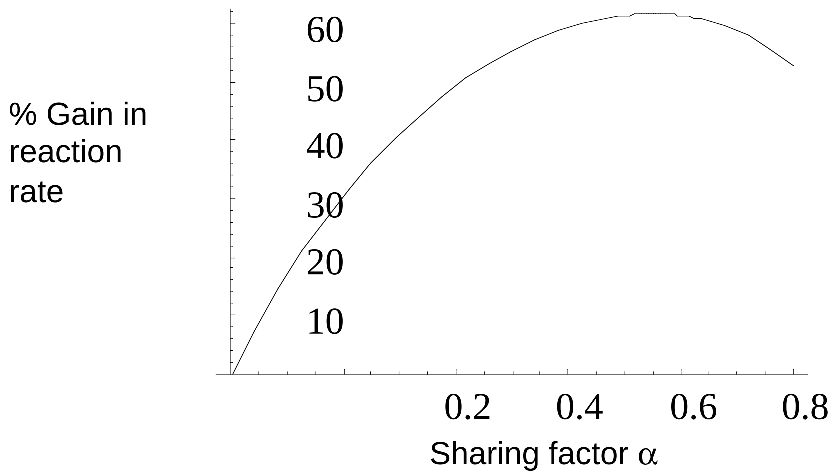
$$q = \frac{[E1]\,K1}{[E1]\,K1 + [E3]\,K3}$$

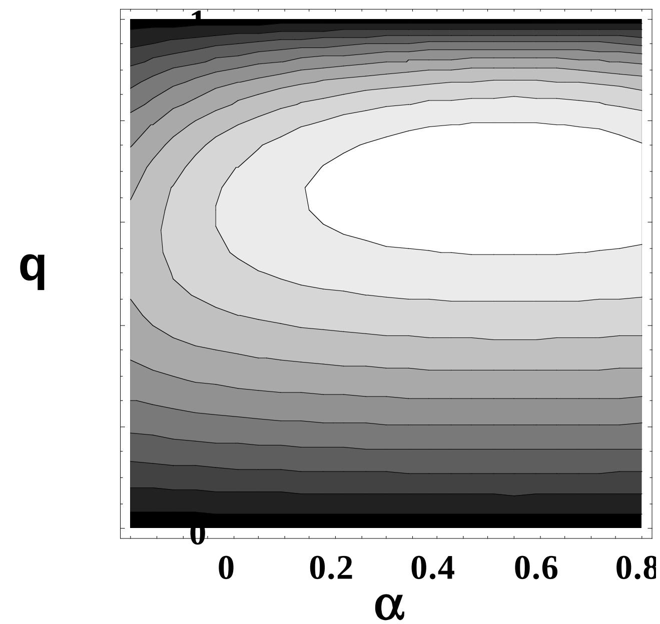
Optimum
(no randomness)



$n_1 = \#(E1)/E2$

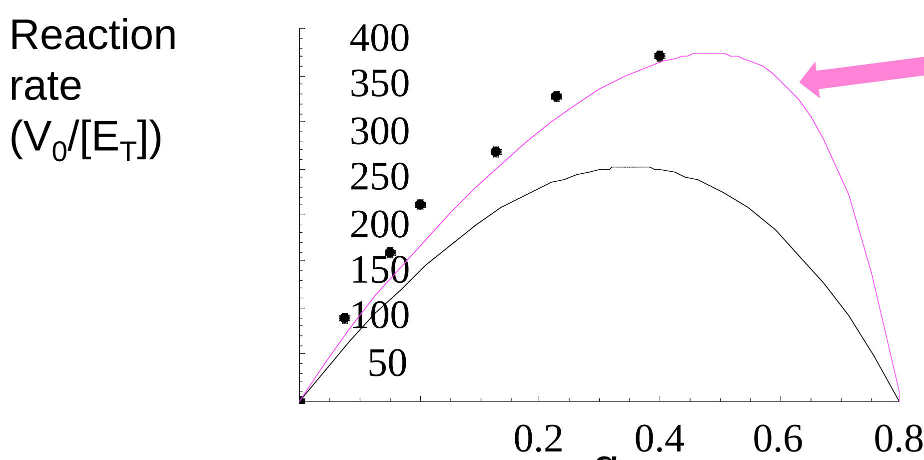
Effect of the enzyme complex composition on the rate of reaction





q = 0.68 ~ 2/3
α = 0.75 = 3/4

Significant values
-2:1 E3K3
-full sharing

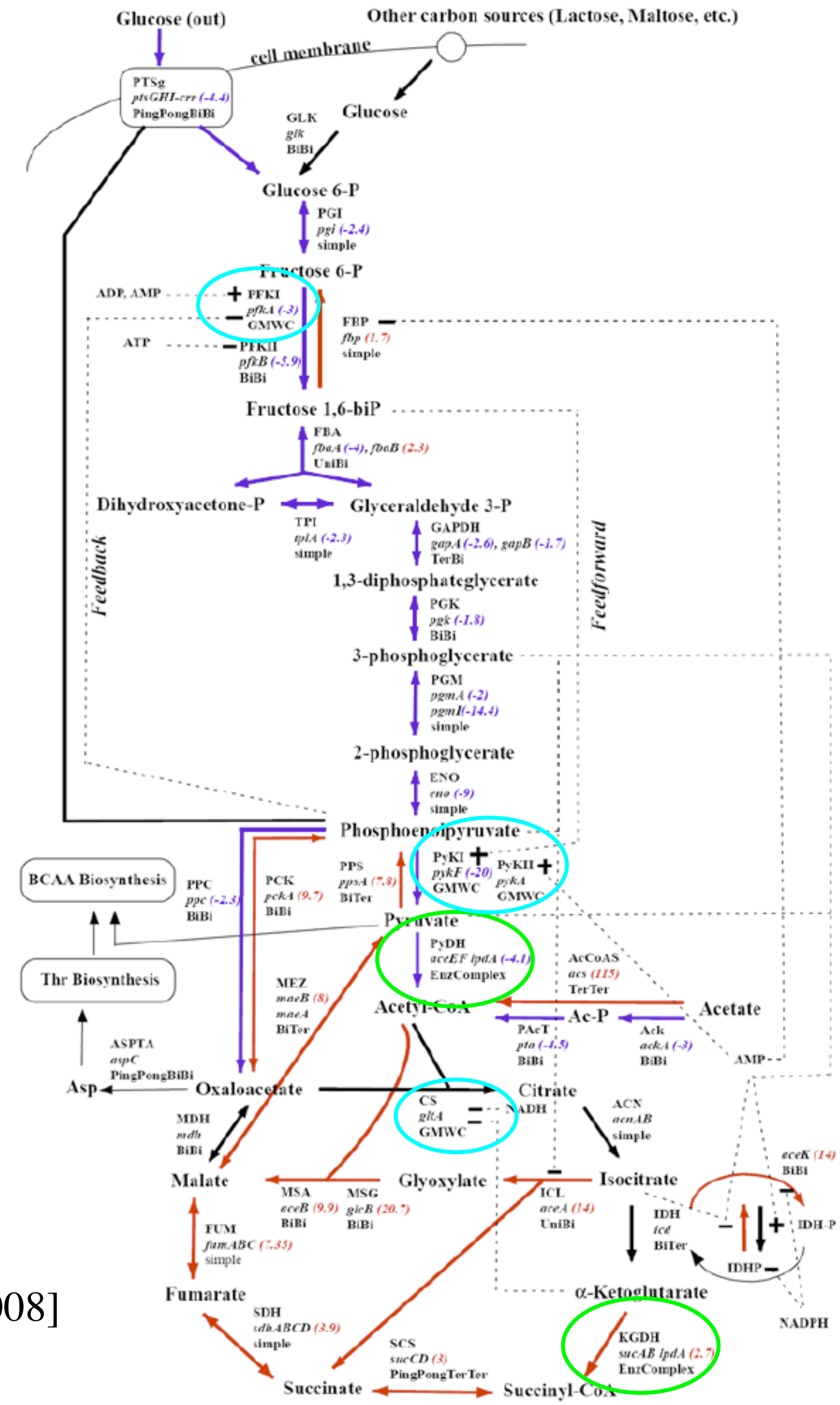


62% increase in rate for α = 0.75

Comparison with literature data

[Danson MJ, Fersht AR, Perham RN, Proc Natl Acad Sci USA. 75(11):5386-90, 1978.]

UCI ICS IGB *SISL*



RSS

GMWC

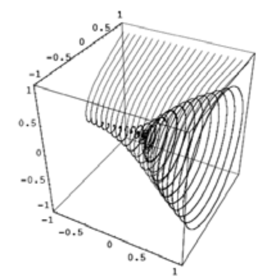
Tarek Najdi, PhD
[ICSB 2007; thesis 2008]

Capture RSS for repetitive use in kMech, Cellerator

```
EnzComplex[{S1_, S2_, S3_} ⇄(En_) {P1_, P2_, P3_},
  Sharing[qq_, aa_], ParamEC[ϵ_, k_, km_]] := With[{},
  answer2[q_, α_] = With[{pmax = 5, mesh = 0.3},
    rate[n1_, s1_, s2_] =
     (k (-3 + n1) n1 s1 (km (-3 + n1) + (-4 + n1) s1) s2 (2 s1 s2 + km (s1 + s2)) ϵ) /
      ((-3 + n1) s1 (km (-3 + n1) + (-4 + n1) s1) s2 (2 s1 s2 + km (s1 + s2)) +
        n1 ((41 + n1 (-22 + 3 n1)) s1^3 s2^2 + km s1^2 s2
             ((-4 + n1) (-10 + 3 n1) s1 + (67 - 40 n1 + 6 n1^2) s2) + km^3 (-3 + n1)^2 (s1^2 + s1 s2 + s2^2) +
           km^2 (-3 + n1) s1 ((-4 + n1) s1^2 + 2 (-7 + 2 n1) s1 s2 + (-13 + 4 n1) s2^2)) ϵ);

    p = Range[pmax];
    λ = Take[{λ1, λ2, λ3, λ4, λ5, λ6, λ7, λ8, λ9, λ10, λ11, λ12}, pmax];
    poly = (1 - n1 / 3) λ.n1^p;
    threewayrate1 =
     Flatten[Table[rate[n1, S1, S2], {S1, 1, 2001, 200}, {S2, 1, 2001, 200}]];
    error = Sum[(poly - threewayrate1)^2, {n1, 0, 3, mesh}];
    numsol = Table[Minimize[error[[i]], λ][[2]], {i, 1, Length[error]}];
    ff[n_] = (1 - n / 3) λ.n^p /. Table[ numsol[[j]], {j, 1, Length[numsol]}];
    ⟨n1⟩ = 3 q;
⟨n1^2⟩ = 3 q + 6 q^2;
⟨n1^3⟩ = 3 q + 18 q^2 + 6 q^3;
⟨n1^4⟩ = 3 q + 42 q^2 + 36 q^3;
⟨n1^5⟩ = 3 q + 90 q^2 + 150 q^3;
    ⟨n1^6⟩ = 3 q + 186 q^2 + 540 q^3;
    rules =
     Flatten@Table[{m0^p -> ⟨n1^p⟩, m1^p -> ⟨n1^p⟩, m2^p -> ⟨n1^p⟩, m3^p -> ⟨n1^p⟩}, {p, 6, 1, -1}];
    Expand[ff[(1 - α) m0 + α (m1 + m2 + m3) / 3]] /. rules
   ];
  list1 = answer2[qq, aa];
  list2 = Flatten[Table[{s1, s2}, {s1, 1, 2001, 200}, {s2, 1, 2001, 200}], 1];
  tbl2 = Table[{list2[[i, 1]], list2[[i, 2]], list1[[i]]}, {i, 1, Length[list1]}];
  app[s1_, s2_] =
   Fit[tbl2, Flatten[Table[Table[s1^k1 s2^k2, {k1, 0, 8}], {k2, 0, 8}]], {s1, s2}];
  {
   P1'[t] == En app[S1[t], S2[t]],
   S1'[t] == -En app[S1[t], S2[t]],
   S2'[t] == -En app[S1[t], S2[t]]
  }
 ]
```

Process simulation using *Mathematica*

- Reactions or generalized reactions
- Computer algebra
  - Representation, eg. of reaction rates
  - Problem-solving environment (PSE)



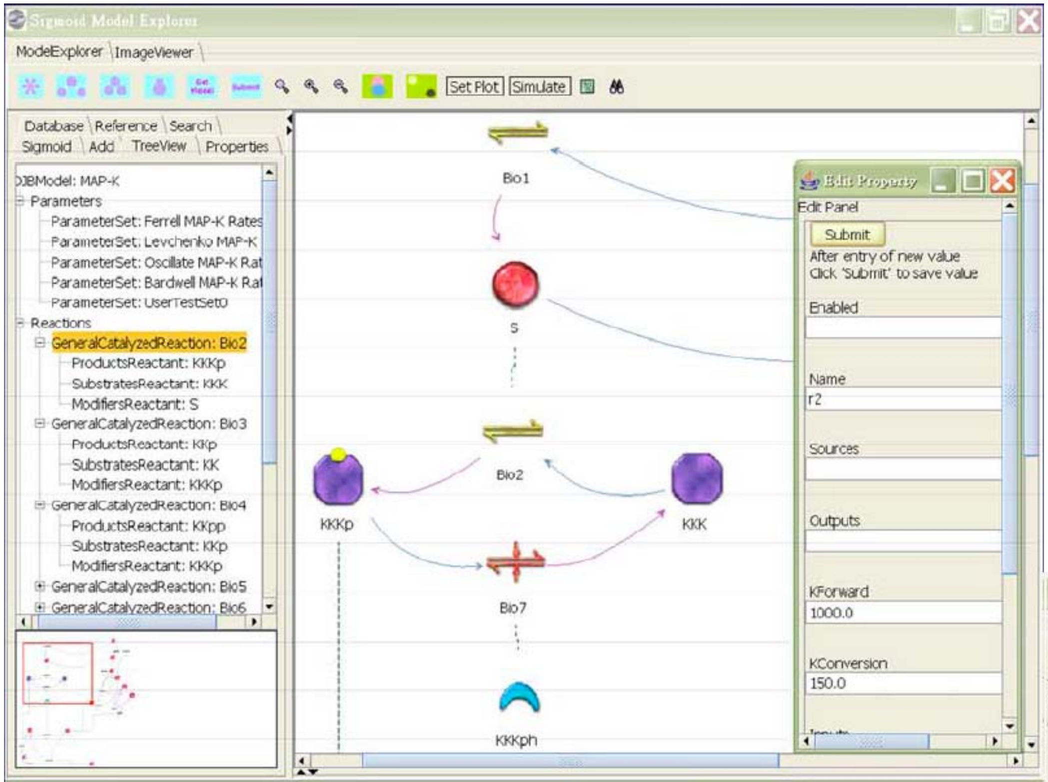
- Special capabilities
  - xCellerator: well developed; fixed reaction schemas
  - Sigmoid: Web GUI, model database
  - Cellzilla: fixed spatial models, power diagrams
  - Plenum: generalized reactions, growing tissues, …

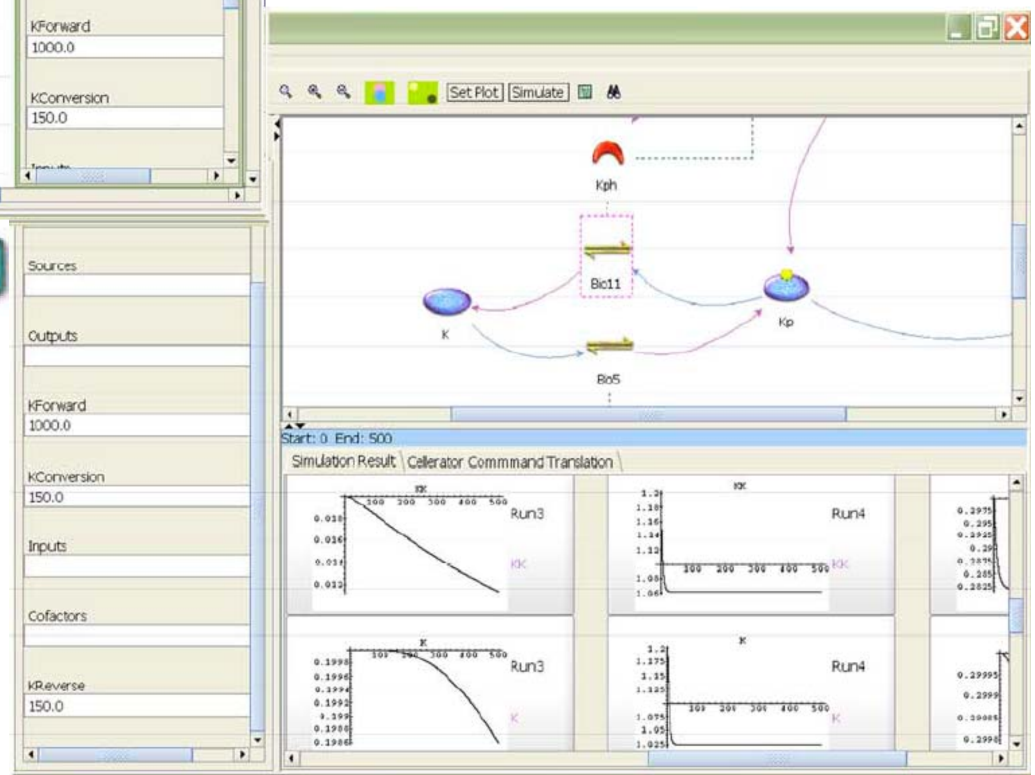
xCellerator addons

- Metabolism: KMech [Yang et al. Bioinformatics 2005]
  - http://www.igb.uci.edu/servers/coli/kmech.html
- Stochastic sim: ssa.m
- Voronoi/power diagrams: mPower.m
- Fixed spatial models: Cellzilla
- Model sources
    - www.cellerator.org (demo.m), www.sigmoid.org

Sigmoid Model Explorer (SME)

- web services
- webstart client





www.sigmoid.org

+ sourceforge

[J. Cheng et al., IEEE Intelligent Systems, May/June 2005]

Sigmoid models web page

(most involve signal transduction)

Institute of Genomics and Bioinformatics

SIGMOID

- Browse Models
- Search Models
  - by Model's Name
  - by Author's Name
  - by Reactant's Name
  - by Reaction's Name
  - by Extended Description
  - by Keyword
  - all Fields
- Search Reactants
- Search Reactions

Models currently available in database:

Models implemented in Sigmoid and Cellerator

- Bardwell_2007_MAPK
- Borghans_1997_CaOscillation_model2
- Borghans_1997_CaOscillation_model3
- Brands_2002_MonosaccharideCasein
- Bullock_and_Fersht_2001_p53
- Chickarmane_2006_StemCellSwitch
- Hilioti_2004_Calcineurin
- Hoffmann_2002_NFKappaB
- Huang_1996_MAPK
- Kholodenko_1999_EGFRsignaling
- MAP-K Demo Reactions
- Markevich_2004_MAPK_orderedElementary
- Markevich_2004_MAPK_orderedMM
- Markevich_2004_MAPK_orderedMM2kinases
- Markevich_2004_MAPK_phosphoRandomElementary
- Markevich_2004_MAPK_phosphoRandomMM
- Markevich_2005_MAPK_AllRandomElementary
- Martins_2003_AmadoriDegradation
- Marwan_2003_Genetics
- Nadji_2006_Asp_Thr_Biosynthesis
- Nielsen_1998_Glycolysis
- Olsen_2003_Peroxidase
- Poolman_2004_Plant Metabolism
- Tyson_1999_CircClock
- Yang_2005_Ile_Val_Leu_AAsynthesis

Models with Cellerator Notebooks

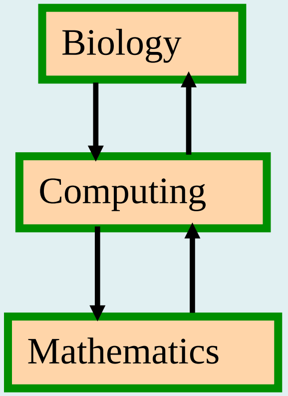
- Algebraic Demo
- Algebraic EnzDemo
- Algebraic EnzDemo
- Algebraic EnzDemo
- Kofahl_2004_Yeast_Pheromone_Pathway
- Zhang_2007_ATM
- Zhang_2007_ATM_MRN_PP2A
- Zhang_2007_Pi3k
- Zhang_2007_SEP

Methods

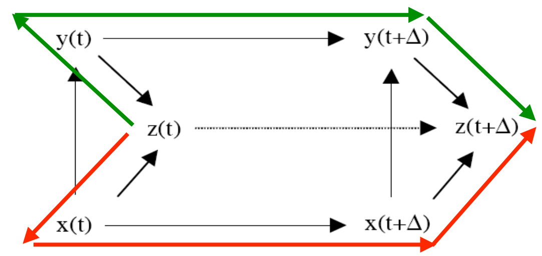
- Partition function algebra
- Composition principle (EMCC)
- Random Steady State (RSS) model

Outline: Math. Methods

- Statistical Mechanics
  - SM in metabolism, transcription
- Stochastic Dynamics
  - Operator algebra
- Classical Spatial Dynamics
  - Hybrid systems; elastic dynamics
- Computational Dynamics
  - Semantics
  - Computational Morphodynamics



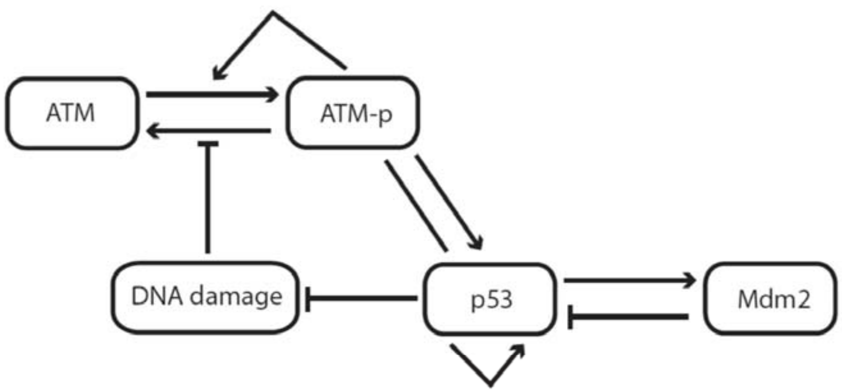
Importance of dynamics



- Scientific understanding
  - Causality
  - Reductionism
  - Dynamical phenotypes
  - Integration across scales
- Necessity for heterogeneous dynamics
  - Metabolism, regulation, mechanics, growth, evo, …
  - Stochastic/deterministic, distributed/global, …

ATM/p53 model

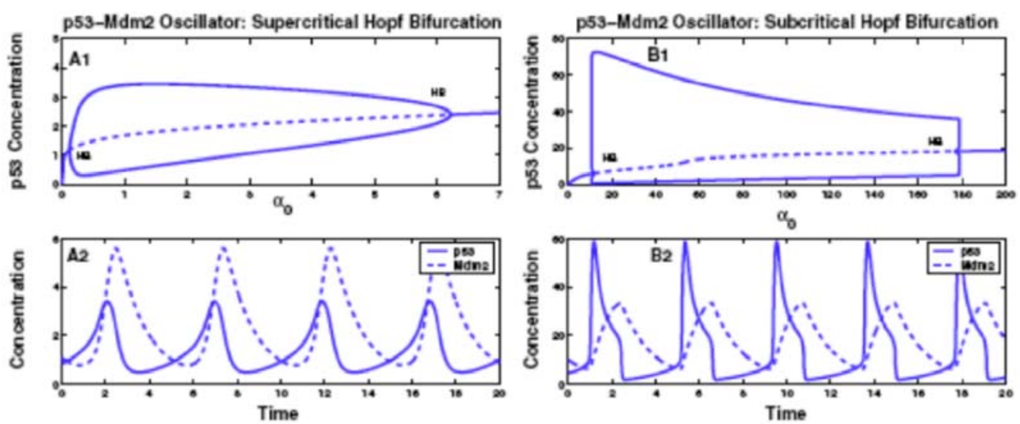
- [Chickarmane et al., J. Applied Dynamical Systems 6:1:61-78, 2007]




```
reactions = {
  {p53 ↦ p53, hill[1, k1, n, 0, α1]},
  {p53 ↦ mdm, hill[1, k2, 4, 0, α3]},
  {p53 + mdm → mdm, γ1},
  {p53 → ∅, γ2}, {mdm → ∅, γ3},
  {∅ → p53, α0}, {∅ → mdm, α2}
 }

odes = interpret[reactions]
```

$$\left\{p53'[t] == \alpha_0 + \frac{p53[t]^n \alpha_1}{p53[t]^n + k_1^n} - mdm[t]\, p53[t]\, \gamma_1 - p53[t]\, \gamma_2,\right.$$

$$\left. mdm'[t] == \alpha_2 + \frac{p53[t]^4 \alpha_3}{p53[t]^4 + k_2^4} - mdm[t]\, \gamma_3,\right\}$$



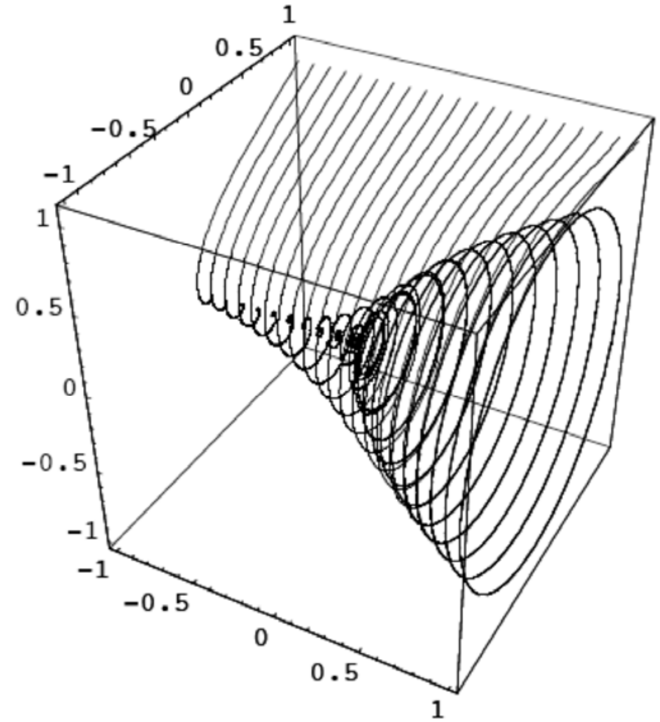
Key feature of interaction:

One system (ATM switch) has its state space partitioned discontinously by flow equivalence classes of the other system (p53 oscillator).

Basic Attractor Structures:

Hopf bifurcation

$$\begin{cases} \dot{x} = -y + x(\mu - x^2 - y^2) \\ \dot{y} = x + y(\mu - x^2 - y^2) \end{cases}$$



Stable, unstable, and center manifolds

Source: [[GuckenheimerHolmes] section 3.2]

- Stable, unstable, center subspaces

$$\frac{dx}{dt} = A \cdot x$$

$$\varphi(x_0, t; A) = x(x_0, t) = e^{tA} x_0$$

$$E^s \equiv \operatorname{span}(v_1, \ldots v_{n_s})$$
$$E^u \equiv \operatorname{span}(u_1, \ldots u_{n_u})$$
$$E^c \equiv \operatorname{span}(w_1, \ldots w_{n_c})$$

$$n_s + n_u + n_c = d$$

- Stable, unstable, center manifolds:

At a hyperbolic fixed point x^*

$$W^s_{\text{loc}} \equiv \left\{ x \in U \,\middle|\, \lim_{t \to +\infty} \varphi(x, t) \to x^* \text{ and } \varphi(x, t) \in U \;\forall\, t \geqslant 0 \right\}$$

$$W^u_{\text{loc}} \equiv \left\{ x \in U \,\middle|\, \lim_{t \to -\infty} \varphi(x, t) \to x^* \text{ and } \varphi(x, t) \in U \;\forall\, t \leqslant 0 \right\}$$

Theorem. **(Center Manifold Theorem for flows).** If $\dot{x} = f(x)$ has a fixed point at x^*, where f has smoothness C^r, then there exist local stable and unstable manifolds W^s and W^u at x^*, with smoothness C^r, and center manifold W^c at x^*, with smoothness C^{r-1}. They are all preserved under the flow of f. They are tangent to E^s, E^u, and E^c respectively, at x^*. Manifolds W^s and W^u are unique, but W^c may not be.

* Homology groups of these manifolds are "invariants"

Equivalence, stability, & normal forms

- C^r Equivalence of dynamical systems

Definition. Given two vector fields f and g, with orbits $\psi^f(x; a, b)$ and corresponding orbits $\psi^g(x; a', b')$ of the form

$$\psi^f(x; a, b) = [\varphi^f(x, t) \,|\, t \in (a, b) \text{ with } a < 0 < b]$$
$$\psi^g(x; a', b') = [\varphi^g(x, t) \,|\, t \in (a', b') \text{ with } a' < 0 < b'],$$

where $\varphi^f(x, t)$ is a solution of the ODE $dx/dt = f(x)$, we say that f and g are "**C^r equivalent**" iff there is a C^r diffeomorphism h that maps each orbit $\psi^f(x; a, b)$ to some orbit $\psi^g(x; a', b')$ and vice versa. C^0 equivalent vector fields are also called "topologically equivalent".

- Structural stability

Definition. Given two vector fields $f \in C^r$ and $g \in C^r$, and nonnegative integers r and k, and a nonnegative real number $\varepsilon > 0$, we say that g is a "C^k, ε ***perturbation*** of f" iff there is some compact set $K \subset \mathbb{R}^d$ such that $f = g$ everywhere except on K, and for all combinations of degrees $j_1, \ldots j_n$ that sum to $i \leqslant k$, the partial derivatives of f and g satisfy:

$$\left| \frac{\partial^i f}{\partial x_1^{j_1} \ldots \partial x_n^{j_n}} - \frac{\partial^i g}{\partial x_1^{j_1} \ldots \partial x_n^{j_n}} \right| < \varepsilon .$$

Definition. A vector field f is **structurally stable** iff there is an $\varepsilon > 0$ such that if g is a C^k, ε perturbation of f, then f and g are C^0 equivalent.

- Normal forms

Theorem. (**Normal form**) If $\dot{x} = f(x)$ has a fixed point at $x^* = 0$, where f has smoothness C^r, then there exists an analytic (C^∞) change of coordinates from x to y such that

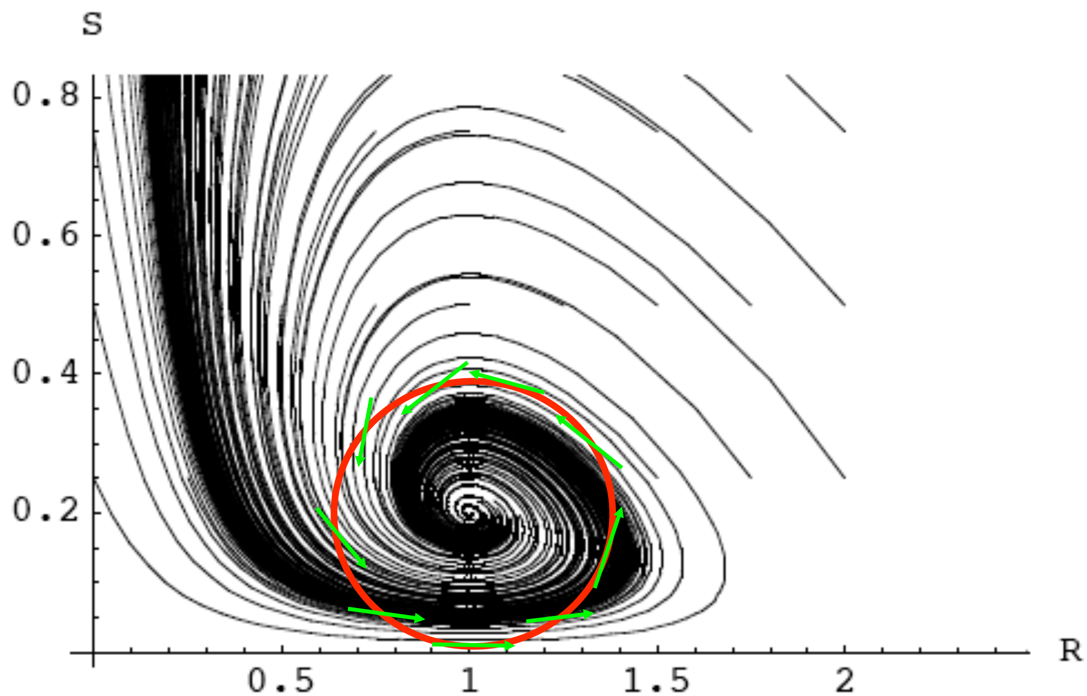
$$\dot{y} = g(y) = \sum_{k=1}^{r} g_k(y) + R_r$$

in an open neighborhood of x^*, where $g_1(y) = L \in H_1$, and for $k \in \{2, r\}$ $g_k(y) \in G_k$, and R_r is $o(|y|^r)$.

Ecology: predator-prey models

- **One Species (finite life span), One Renewable Resource**

```
species3 = {{S + R → 2 S, 0.5}, {S → ∅, 0.5}, {∅ → R, 0.1}}
```



Index=+1

… as for all 2D sinks, sources, centers.

Generalization:

*n*D index; degree theory

with Elaine Wong, UCI

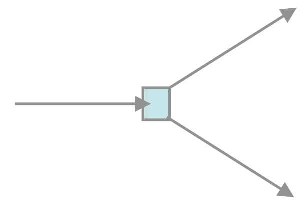
Indexes in p53 model: [Golubyatnikov & Mjolsness BGRS 2008]

Methods

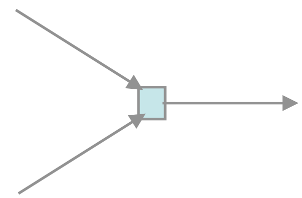
- Operator algebra
- Time-ordered Product Expansion
- Rejection sampling

Elementary Reactions

- $A \rightarrow B + C$ with rate k_f



- $B + C \rightarrow A$ with rate k_r



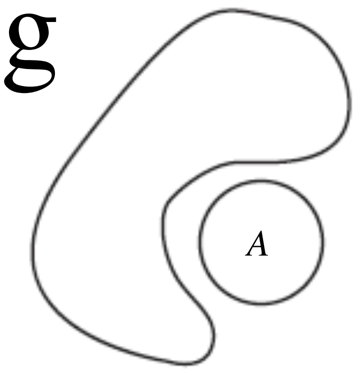
- Effective conservation laws

  E.g. $N_A + N_B$, $N_A + N_C$ if A, B, C are different

- $A \equiv C$ => A regulates B, supplying only *information*,

  denoted $A \mapsto B$

E.g. Binding and unbinding



A + unoccupied_site <---> occupied_site

Equilibrium:

$$Z(z_A) = 1 + \omega_A z_A$$

$$p_{\text{occupied}} = \frac{\omega_A z_A}{1 + \omega_A z_A} = \frac{\partial \log Z(z_A)}{\partial \log z_A}$$

Dynamics:

Let molecular species A bind and unbind at a particular molecular binding site, from a solution with many molecules of A available. For very small times Δt only one such event will happen if any, so

$$\Pr(\text{unoccupied} \to \text{occupied} \mid \Delta t) = \alpha \Delta t [A]$$
$$\Pr(\text{occupied} \to \text{unoccupied} \mid \Delta t) = \beta \Delta t$$

n_A =# of A's bound to site = 0 or 1.

Master equation

$$\frac{d}{dt}\begin{pmatrix} p_{n=0} \\ p_{n=1} \end{pmatrix} = \begin{pmatrix} -\alpha[A]\, p_{n=0} + \beta\, p_{n=1} \\ \alpha[A]\, p_{n=0} - \beta\, p_{n=1} \end{pmatrix} = H \begin{pmatrix} p_{n=0} \\ p_{n=1} \end{pmatrix}$$

$$H = \begin{pmatrix} -\alpha[A] & \beta \\ \alpha[A] & -\beta \end{pmatrix}; \quad \text{want} \quad e^{tH}.$$

Binding/unbinding solution

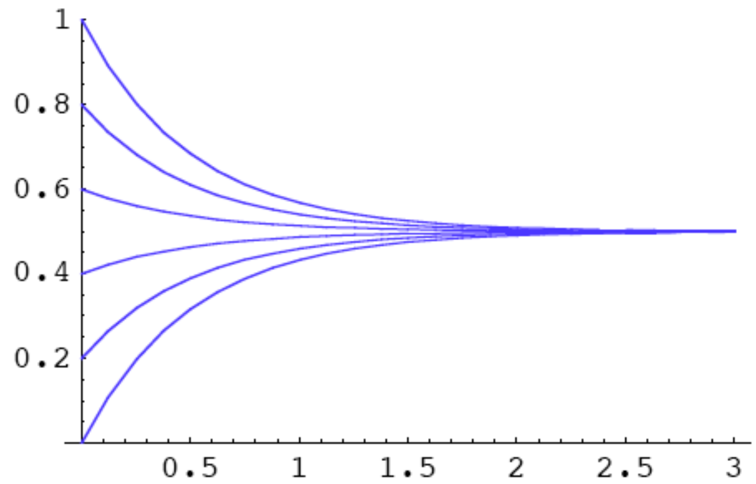
Solution: There is an *algebra* of H's:

$$(-H)^k = -(\alpha[A] + \beta)^{k-1}\, H \quad (\text{for } k > 0)$$

so

$$\begin{aligned} \begin{pmatrix} p_{n=0}(t) \\ p_{n=1}(t) \end{pmatrix} &= e^{t\,H} \begin{pmatrix} p_{n=0}(0) \\ p_{n=1}(0) \end{pmatrix} \\ &= \frac{1}{\alpha[A]+\beta} \begin{pmatrix} \beta \\ \alpha[A] \end{pmatrix} + \frac{\alpha[A]\,p_0 - \beta\,p_1}{\alpha[A]+\beta}\, e^{-t\,(\alpha[A]+\beta)} \begin{pmatrix} 1 \\ -1 \end{pmatrix} . \end{aligned}$$

Convergence to Hill function $\frac{\alpha[A]}{\alpha[A]+\beta}$:



Powers of basis operators

$$\hat{a} = \begin{pmatrix} 0 & 0 & 0 & 0 & \cdots \\ 1 & 0 & 0 & 0 & \\ 0 & 1 & 0 & 0 & \\ 0 & 0 & 1 & 0 & \\ \vdots & & & \ddots & \ddots \end{pmatrix}; \ \hat{a}^2 = \begin{pmatrix} 0 & 0 & 0 & 0 & \cdots \\ 0 & 0 & 0 & 0 & \\ 1 & 0 & 0 & 0 & \\ 0 & 1 & 0 & 0 & \\ \vdots & & \ddots & & \ddots \end{pmatrix}; \ \hat{a}^3 = \begin{pmatrix} 0 & 0 & 0 & 0 & \cdots \\ 0 & 0 & 0 & 0 & \\ 0 & 0 & 0 & 0 & \\ 1 & 0 & 0 & 0 & \\ \vdots & \ddots & & & \ddots \end{pmatrix}; \ \ldots$$

$$[\hat{a}^k]_{n\,m} = \delta_{n,m+k}$$

$$a = \begin{pmatrix} 0 & 1 & 0 & 0 & 0 & \cdots \\ 0 & 0 & 2 & 0 & 0 & \\ 0 & 0 & 0 & 3 & 0 & \\ 0 & 0 & 0 & 0 & 4 & \\ \vdots & & & & \ddots & \ddots \end{pmatrix}; \ a^2 = \begin{pmatrix} 0 & 0 & 2 & 0 & 0 & \cdots \\ 0 & 0 & 0 & 6 & 0 & \\ 0 & 0 & 0 & 0 & 12 & \\ 0 & 0 & 0 & 0 & 0 & \ddots \\ \vdots & & & & & \ddots \end{pmatrix}; \ a^3 = \begin{pmatrix} 0 & 0 & 0 & 6 & 0 & \cdots \\ 0 & 0 & 0 & 0 & 24 & \\ 0 & 0 & 0 & 0 & 0 & \ddots \\ 0 & 0 & 0 & 0 & 0 & \\ \vdots & & & & & \ddots \end{pmatrix}; \ \ldots$$

$$\left[a^k\right]_{n\,m} = (m)_k\,\delta_{n,m-k} = \frac{m!}{(m-k)!}\,\delta_{n,m-k}$$

Compare to:

$$z^k\, z^m = z^{m+k} \quad \text{and} \quad \partial_z{}^k\, z^m = (m)_k\, z^{m-k}$$

Example: $\left\{ \varnothing \xrightarrow{\rho_i} \mathrm{A} \right\}$

$H = \rho\,(\hat{a} - I)$ Because $[\hat{a}, I] = 0$,

$$\exp t\,H = \exp(\rho\,t\,(\hat{a} - I)) = \exp(-\rho\,t\,I)\exp\ \rho\,t\ \hat{a}$$

$$= e^{-\rho\,t} \sum_{n=0}^{\infty} \frac{(\rho\,t)^n}{n\,!}\,\hat{a}^n$$

$$= e^{-\rho\,t} \begin{pmatrix} 1 & 0 & 0 & 0 & 0 & \cdots \\ \rho\,t & 1 & 0 & 0 & 0 & \ddots \\ \frac{(\rho\,t)^2}{2\,!} & \rho\,t & 1 & 0 & 0 & \ddots \\ \frac{(\rho\,t)^3}{3\,!} & \frac{(\rho\,t)^2}{2\,!} & \rho\,t & 1 & 0 & \ddots \\ \frac{(\rho\,t)^4}{4\,!} & \frac{(\rho\,t)^3}{3\,!} & \frac{(\rho\,t)^2}{2\,!} & \rho\,t & 1 & \ddots \\ \vdots & \ddots & \ddots & & \ddots & \ddots \end{pmatrix}$$

Operator Algebra Translation

- Reaction net: $\{\mathrm{m}_i^{(r)}\,\mathrm{A}_i\} \xrightarrow{\mathrm{k}^{(r)}} \{\mathrm{n}_i^{(r)}\,\mathrm{A}_i\}$

- Translation: $$H = \sum_{r=1}^{R} k^{(r)} \left[\left(\prod_{i=1}^{I} (\hat{a}_i)^{n_i^{(r)}} \right) \left(\prod_{i=1}^{I} (a_i)^{m_i^{(r)}} \right) - \prod_{i=1}^{I} (N_i)_{m_i^{(r)}} \right]$$

$$H = \sum_r O_r = \sum_r \hat{O}_r - \sum_r D_r \equiv \hat{H} - D$$

- S-E-P Example: $\mathtt{auxin[i]} \xRightarrow{\mathtt{PIN1[i,j]}} \mathtt{auxin[j]}$

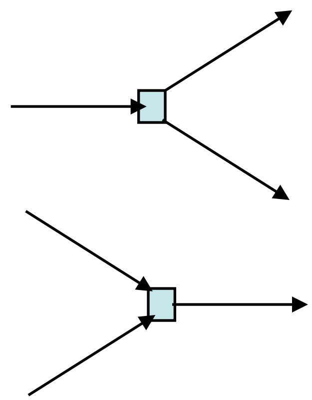
$$k_f\,(\hat{a}_3\, a_1\, a_2 - N_1\, N_2) + k_{r1}\,(\hat{a}_1\, \hat{a}_2\, a_3 - N_3) + k_d\,(\hat{a}_1\, \hat{a}_4\, a_3 - N_3) + k_{r2}\,(\hat{a}_3\, a_1\, a_4 - N_1\, N_4)$$

- Simulation:

$$\frac{d}{dt} \Pr(t \mid 0) = H \Pr(t \mid 0)$$

$$\Pr(t \mid 0) = e^{tH} \Pr(0) \qquad e^{tH} = \lim_{n \to \infty} \left(1 + \frac{t}{n} H\right)^n$$

Elementary Processes



- $A(x) \rightarrow B(y) + C(z)$ **with** $\rho_f(x, y, z)$
- $B(y) + C(z) \rightarrow A(x)$ **with** $\rho_r(y, z, x)$
- Examples
  - Chemical reaction networks w/o params
  - $\text{HydrogenAtom}(x), \text{HydrogenAtom}(y) \rightarrow \text{HydrogenMolecule}(z)$
    $$\textbf{with } f(\|x-y\|)\exp\left(-\left(\|x-z\|^2+\|y-z\|^2\right)/2\sigma^2\right)$$
  - $\{bacterium(x),\ macrophage(y)\} \rightarrow macrophage(y)$ **with** $\rho(\|x-y\|)$
- Effective conservation laws
  - E.g. $\int N_A(x)\,dx + \int N_B(y)\,dy$,
    $\int N_A(x)\,dx + \int N_C(z)\,dz$

Elementary process *algebra*

$$A_1(x_1),\, A_2(x_2),\ \ \ldots,\, A_n(x_n) \to B_1(y_1),\, B_2(y_2),\ \ \ldots,\, B_m(y_m)\ \textbf{with}\ \rho(\{x_i\},\, \{y_j\})$$

- Composition is by independent parallelism
- Dynamics from the **Master Equation**:

$$\frac{d\mathbf{p}}{dt} = \Big(\sum_{processes,r} W_r\Big) \cdot \mathbf{p}$$

- Create elementary processes from yet more elementary "Basis operators"
  - Term creation/annihilation operators: for each param value,

$$\hat{a} = \begin{pmatrix} 0 & 0 & 0 & 0 & \cdots \\ 1 & 0 & 0 & 0 & \\ 0 & 1 & 0 & 0 & \\ 0 & 0 & 1 & 0 & \\ \vdots & & & \ddots & \ddots \end{pmatrix} = \delta_{n,m+1} \ \text{ and } a = \begin{pmatrix} 0 & 1 & 0 & 0 & \cdots \\ 0 & 0 & 2 & 0 & \\ 0 & 0 & 0 & 3 & \\ 0 & 0 & 0 & 0 & \ddots \\ \vdots & & & & \ddots \end{pmatrix} = m\,\delta_{n+1,m}$$

$$[a,\ \hat{a}] \equiv (a\ \hat{a} - \hat{a}\, a) = I$$

  - Obeying Heisenberg **operator algebra**

$$[a(x),\ \hat{a}(y)] = \delta(x-y)\Big[I + N\, Q\big(N \,\big|\, n^{(\max)}\big)\Big]$$

  - Yet classical, not quantum, probabilities

[Annals of Math. and A. I., 47(3-4), January 2007]

A general solution method

… for recursion equations of small reaction nets

- Generating function

$$G_{\{m\}}(\{z\}, t) = \sum_{\{n(i)=0\}}^{\infty} \mathrm{Pr}_{\{n(i)\},\{m(i)\}}(t) \prod_i (z_i)^{n(i)} \qquad G_{\{m\}}(\{z\}, 0) = \prod_i (z)^{m(i)}$$

- Operator algebra representation

$$a_i \mapsto \partial_{z(i)} \equiv \frac{\partial}{\partial z_i}, \;\; \hat{a}_i \mapsto z_i, \;\; I \mapsto 1, \;\; N_i = \hat{a}_i\, a_i \mapsto z_i\, \partial_{z(i)}, \;\; \text{and } [a_i, \hat{a}_j] = \delta_{i\,j}$$

- Context-free grammar ⇒ first order linear PDE

Example: $\left\{ \mathrm{A} \xrightarrow{\rho_\mathrm{d}} \varnothing \right\}$

Operator: $$H = \rho\,(a - N)$$

PDE: $$\frac{d}{d\,t}\,G_m(z,\,t) = H\,G_m(z,\,t) = \rho\left(\frac{\partial}{\partial z} - z\,\frac{\partial}{\partial z}\right)G_m(z,\,t) = \rho(1-z)\,\frac{\partial}{\partial z}\,G_m(z,\,t)$$

Solution:

$$G_m(z,\,t) = ((z-1)\,e^{-\rho\,t} + 1)^m = \sum_{n=0}^{m}\binom{m}{n}e^{-n\,\rho\,t}(1-e^{-\rho\,t})^{m-n}\,z^n,\; n \sim \mathrm{Binomial}(m,\,e^{-\rho\,t})$$

Example: $\{A \xrightarrow{k_f} B,\ B \xrightarrow{k_r} A\}$

- Operator: $$H = k_f\,(\hat{a}_2\,a_1 - N_1\,I_2) + k_r\,(\hat{a}_1\,a_2 - I_1\,N_2)$$
- PDE: $$[k_r\,(z_2 - z_1)\,(\partial_2 - \kappa\,\partial_1) - \lambda]\,g_{\{m\}\,\lambda}\,(z) = 0$$
- IC: $$\int g_{\{m\}\,\lambda}\,(z)\,d\lambda = z_1^{m(1)}\ z_2^{m(2)}$$
- Change variables: $$g_{\{m\}\,\lambda}\,(z) = z_1^{m(1)}\ z_2^{m(2)}\ g_\lambda\,(\zeta),\quad \zeta = z_1\,/\,z_2$$
- PDE: $$[k_r\,(1 - \zeta)\,((m_2\,\zeta - m_1\,\kappa) - (\zeta + \kappa)\,\partial_\zeta) - \lambda\zeta]\,g_{\{m\}\,\lambda}\,(\zeta) = 0$$
- Solution: $$\mathrm{DSolve}[((1-\zeta)\,(m_2\,\zeta - m_1\,\kappa)\,k_r\,)\,g_m[\zeta,\,t] - (1-\zeta)\,(\zeta+\kappa)\,k_r\,\partial_\zeta\,g_m[\zeta,\,t] == -\zeta\,\partial_t\,g_m[\zeta,\,t],\ g_m[\zeta,\,t],\ \{\zeta,\,t\}]$$ $$\Big\{\Big\{g_m[\zeta,\,t] \to e^{\zeta\,m_2}\,(\zeta+\kappa)^{-\kappa\,(m_1+m_2)}\,C[1]\Big[\frac{-\mathrm{Log}[-1+\zeta] - \kappa\,\mathrm{Log}[\zeta+\kappa] + t\,k_r + t\,\kappa\,k_r}{(1+\kappa)\,k_r}\Big]\Big\}\Big\}$$
- Impose IC's: $$g_{\{m\}}(\zeta,\,t) = e^{m_2(\zeta - \varphi(\zeta,t))}\left(\frac{\varphi(\zeta,\,t) + \kappa}{\zeta + \kappa}\right)^{\kappa\,(m_1+m_2)}$$ $$\psi_{\kappa,k_r}\,(\zeta) = \log(\zeta - 1) + \kappa\log(\zeta + \kappa)$$ $$\psi_{\kappa,k_r}\,(\varphi(\zeta,\,t)) = -(1+\kappa)\,k_r\,t + \psi_{\kappa,k_r}\,(\zeta)$$

Example: $\left\{A \xrightarrow{\rho_b} 2A,\ \varnothing \xrightarrow{\rho_i} A,\ A \xrightarrow{\rho_d} \varnothing\right\}$

- Operator: $H = \rho_b\left(\hat{a}^2\, a - N\right) + \rho_d\,(a - N) + \rho_i\,(\hat{a} - I)$
- PDE: $\frac{d}{d\,t} G_m(z,t) = H\, G_m(z,t) = \left(\rho_i\,(z-1) + \left(\rho_b\, z^2 - (\rho_b + \rho_d)\,z + \rho_d\right)\frac{\partial}{\partial z}\right) G_m(z,t) = \lambda\, G_m(z,t)$
- IC: $G_{\{m\}}(\{z\},0) = \prod_i (z)^{m(i)}$
- Solution:

$$\mathrm{DSolve}\left[\frac{\partial g_m(z,t)}{\partial t} == \rho_3\,(z-1)\,g_m(z,t) + \left(\rho_1\, z^2 - (\rho_1+\rho_2)\,z + \rho_2\right)\frac{\partial g_m(z,t)}{\partial z},\ g_m(z,t),\ \{z,t\}\right]$$

$$\left\{\left\{g_m[z,t] \to (z\,\rho_1 - \rho_2)^{-\frac{\rho_3}{\rho_1}}\, C\left[\frac{\mathrm{Log}[-1+z] - \mathrm{Log}[z\,\rho_1 - \rho_2] + t\,\rho_1 - t\,\rho_2}{\rho_1 - \rho_2}\right]\right\}\right\}$$

- Impose IC's:

(Galton-Watson solution;

semigroup rep.)

$$G_m(z,t) = \left(\frac{(\rho_b - \rho_d)}{\rho_b(1 - e^{(\rho_b-\rho_d)\,t})\,z + (\rho_b\, e^{(\rho_b-\rho_d)\,t} - \rho_d)}\right)^{\rho_i/\rho_b}$$

$$\left(\frac{(\rho_b - \rho_d\, e^{(\rho_b-\rho_d)\,t})\,z + \rho_d(e^{(\rho_b-\rho_d)\,t} - 1)}{\rho_b(1 - e^{(\rho_b-\rho_d)\,t})\,z + (\rho_b\, e^{(\rho_b-\rho_d)\,t} - \rho_d)}\right)^m.$$

Example: $\left\{ \mathrm{A} + \mathrm{B} \xrightarrow{k_f} \mathrm{C},\ \mathrm{C} \xrightarrow{k_r} \mathrm{A} + \mathrm{B} \right\}$

- Operator: $H = k_f\,(\hat{a}_3\, a_1\, a_2 - N_1\, N_2\, I_3) + k_r\,(\hat{a}_1\, \hat{a}_2\, a_3 - I_1\, I_2\, N_3)$
- PDE: $[k_r\,(z_3 - z_1\, z_2)\,(\partial_3 - \kappa\,\partial_1\,\partial_2) - \lambda]\, g_{\{m\}\,\lambda}(z) = 0$
- IC: $\int g_{\{m\}\,\lambda}(z)\, d\lambda = z_1^{m(1)}\, z_2^{m(2)}\, z_3^{m(3)}$
- Change of variable: $g_{\{m\}\,\lambda}(z) = z_1^{m(1)}\, z_2^{m(2)}\, z_3^{m(3)}\, g_\lambda(\zeta),\ \ \zeta = z_1\, z_2 / z_3$
- PDE: $k_r[(1/\zeta - 1)\,(\zeta(m_3 - \partial_\zeta) - \kappa\,(m_1 + \partial_\zeta)\,(m_2 + \partial_\zeta)) - \lambda']\, g_\lambda(\zeta) = 0$
- Steady state: $(\partial_{\zeta\zeta} + (m_1 + m_2 - \zeta)\,\partial_\zeta - \zeta\, m_3 / \kappa + m_1\, m_2)\, g_\lambda(\zeta) = 0$

$$\mathbf{LSS} = \mathbf{m}_1\, \mathbf{m}_2\, \mathbf{g}_0[\xi] - \xi\,(\mathbf{m}_3/\kappa)\, \mathbf{g}_0[\xi] - \xi\, \mathbf{g}_0'[\xi] + \kappa\, \mathbf{m}_1\, \mathbf{g}_0'[\xi] + \kappa\, \mathbf{m}_2\, \mathbf{g}_0'[\xi] + \mathbf{g}_0''[\xi]$$

$$\mathtt{DSolve}[\mathbf{LSS} == 0,\ \mathbf{g}_0[\xi],\ \xi]$$

- Sol'n: $\Big\{\Big\{ g_0[\zeta] \to e^{-\frac{\zeta m_3}{\kappa}}\, C[1]\, \mathrm{HermiteH}\Big[\frac{\kappa^2 m_1 m_2 - \kappa^2 m_1 m_3 - \kappa^2 m_2 m_3 + m_3^2}{\kappa^2},\ \frac{\zeta}{\sqrt{2}} - \frac{\kappa^2 m_1 + \kappa^2 m_2 - 2 m_3}{\sqrt{2}\,\kappa}\Big] + e^{-\frac{\zeta m_3}{\kappa}}$
$C[2]\, \mathrm{Hypergeometric1F1}\Big[-\frac{\kappa^2 m_1 m_2 - \kappa^2 m_1 m_3 - \kappa^2 m_2 m_3 + m_3^2}{2\kappa^2},\ \frac{1}{2},\ \Big(\frac{\zeta}{\sqrt{2}} - \frac{\kappa^2 m_1 + \kappa^2 m_2 - 2 m_3}{\sqrt{2}\,\kappa}\Big)^2\Big]\Big\}\Big\}$

New since 2006:

Nonstationary Partial Solution, A+B <--> C

- Drop first of four terms. Solve:

```
DSolve[
 (z^2 D[ψ[z], {z, 2}] - ((α + β - 1) z + κ (1 - z)) D[ψ[z], {z, 1}] + (α β + λ) ψ[z] == 0), ψ[z], z]
```

$$\Big\{\Big\{\psi[z] \to \left(\frac{1}{z}\right)^{\frac{1}{2}\left(-\alpha-\beta+\kappa-\sqrt{(\alpha+\beta-\kappa)^2-4(\alpha\beta+\lambda)}\right)} \kappa^{\frac{1}{2}\left(-\alpha-\beta+\kappa-\sqrt{(\alpha+\beta-\kappa)^2-4(\alpha\beta+\lambda)}\right)} \mathrm{C[1]\ Hypergeometric1F1}\Big[-\frac{\alpha}{2}-\frac{\beta}{2}+\frac{\kappa}{2}-\frac{1}{2}\sqrt{(\alpha+\beta-\kappa)^2-4(\alpha\beta+\lambda)},\ 1-\sqrt{(\alpha+\beta-\kappa)^2-4(\alpha\beta+\lambda)},\ -\frac{\kappa}{z}\Big] +$$
$$\left(\frac{1}{z}\right)^{\frac{1}{2}\left(-\alpha-\beta+\kappa+\sqrt{(\alpha+\beta-\kappa)^2-4(\alpha\beta+\lambda)}\right)} \kappa^{\frac{1}{2}\left(-\alpha-\beta+\kappa+\sqrt{(\alpha+\beta-\kappa)^2-4(\alpha\beta+\lambda)}\right)} \mathrm{C[2]\ Hypergeometric1F1}\Big[-\frac{\alpha}{2}-\frac{\beta}{2}+\frac{\kappa}{2}+\frac{1}{2}\sqrt{(\alpha+\beta-\kappa)^2-4(\alpha\beta+\lambda)},\ 1+\sqrt{(\alpha+\beta-\kappa)^2-4(\alpha\beta+\lambda)},\ -\frac{\kappa}{z}\Big]\Big\}\Big\}$$

- Use TOPE (perturbation theory) to add first term back in, with forward reaction events
- Great acceleration possible far from equilibrium (as life often is).

Example: $\{\mathbf{A} + \mathbf{B} \rightleftharpoons \mathbf{C} \rightleftharpoons \mathbf{A} + \mathbf{D}\}$

- Operator:

$$H = k_f\,(\hat{a}_3\, a_1\, a_2 - N_1\, N_2) + k_{r1}\,(\hat{a}_1\, \hat{a}_2\, a_3 - N_3) + k_d\,(\hat{a}_1\, \hat{a}_4\, a_3 - N_3) + k_{r2}\,(\hat{a}_3\, a_1\, a_4 - N_1\, N_4)$$

- Change of variable:

$$g_{\{m\}\lambda}(z) = z_1^{m(1)}\, z_2^{m(2)}\, z_3^{m(3)}\, z_4^{m(4)}\, g_{\{m\}\lambda}(\zeta_1,\ \zeta_2)$$
$$\zeta_1 = z_1\, z_2 / z_3,\ \zeta_2 = z_1\, z_4 / z_3$$

$$g_{\{m\}\lambda}(z) = z_1^{m(1)}\, z_2^{m(2)}\, z_3^{m(3)}\, z_4^{m(4)}\, g_{\{m\}\lambda}(\zeta_1,\ \zeta_2)$$
$$\zeta_1 = \sqrt{z_4 / z_2},\ \zeta_2 = z_3 \big/ \left(z_1 \sqrt{z_2\, z_4}\right)$$

- PDE:

$$\begin{aligned}
&[(1-\zeta_1)\,(k_{r1}\,\zeta_1\,(m_3 - \partial_{\zeta_1}) - k_f\,(m_1 + \partial_{\zeta_1})\,(m_2 + \partial_{\zeta_1})) + \\
&-(1-\zeta_1)\,(k_{r1}\,\zeta_1\,\partial_{\zeta_2} + k_f\, m_2\,\partial_{\zeta_2} + k_f\,\partial_{\zeta_1}\,\partial_{\zeta_2}) \\
&+ (1-\zeta_2)\,(k_d\,\zeta_2(m_3 - \partial_{\zeta_1} - \partial_{\zeta_2}) - k_{r2}\,(m_1 + \partial_{\zeta_1} + \partial_{\zeta_2})\,(m_4 + \partial_{\zeta_2})) \\
&- (1-\zeta_2)\,(k_d\,\zeta_2\,\partial_{\zeta_1} + k_{r2}\, m_4\,\partial_{\zeta_1} + k_{r2}\,\partial_{\zeta_1}\,\partial_{\zeta_2}) - \lambda\zeta_1\,\zeta_2]\, g_{\{m\}\lambda}(\zeta_1,\ \zeta_2) = \\
&0\,.
\end{aligned}$$

- **Problem**: treat sol'n as a special function?

Problem: Composition of reaction network solutions

- Could special solutions e.g. to $\{A + B \rightleftharpoons C \rightleftharpoons A + D\}$ *composed* into approximate solutions of larger networks?
- Can we *decompose H* into a sum of solvable and simulable parts, then use perturbation theory (including Feynman diagrams) to simulate more efficiently? To analyse more effectively?
- Yes: Operator algebra TOPE shows how.

Dynamics of moments

- Master equation $\frac{d}{dt}\Pr(t) = H\Pr(t)$ $\quad \{m_i^{(r)} A_i\} \xrightarrow{k^{(r)}} \{n_i^{(r)} A_i\}$
- Moments $\left\langle \prod_{\sigma=1}^{k} n_{i(\sigma)} \right\rangle = \mathbf{1}^{T} \cdot \prod_{\sigma=1}^{k} N_{i(\sigma)} \cdot \Pr(t)$
- Dynamics: $\frac{d}{dt}\left\langle \prod_i (n_i)_{k(i)} \right\rangle =$
$$\sum_{r=1}^{R} k^{(r)} \sum_{\{p(i)=0\}}^{\{k(i)\}} \left[\left(\prod_{i=1}^{I} \frac{\left(n_i^{(r)}\right)_{p(i)} (k(i))_{p(i)}}{p(i)!} \right) - \left(\prod_{i=1}^{I} \frac{\left(m_i^{(r)}\right)_{p(i)} (k(i))_{p(i)}}{p(i)!} \right) \right] \left\langle \prod_{i=1}^{I} (n_i)_{m_i^{(r)}+k(i)-p(i)} \right\rangle$$
- Monomial rep: ***problem*** in Stirling numbers
- Means only = mass action: $\frac{d\langle n_i\rangle}{dt} = \sum_{r=1}^{R} k^{(r)} \left(n_i^{(r)} - m_i^{(r)}\right) \prod_j \langle n_j \rangle^{m_j^{(r)}}$
- **Problem**: find a useful, probability-conserving cutoff beyond the means.

Methods

- Operator algebra
- Time-ordered Product Expansion
- Rejection sampling

Generation of valid algorithms

- Compute or sample exp $t\,H$; e.g. Euler's formula

$$e^{tH} = \lim_{n\to\infty}\left(1+\frac{t}{n}H\right)^n$$

- Approximate: Trotter Product formula

$$= \lim_{n\to\infty}\left[e^{(t/n)H_0}\ e^{(t/n)H_1}\right]^n$$

- Second-order operator splitting
- CBH formula

$$\exp(tH_0)\exp(tH_1) = \exp\left(tH_0 + tH_1 + \frac{t^2}{2}[H_0,H_1] + \frac{t^3}{12}[H_0,[H_0,H_1]] - \frac{t^3}{12}[H_1,[H_0,H_1]] + O(t^4)\right)$$

- Time-ordered product expansion (TOPE)

$$\exp(t\,H)\cdot p_0 = \exp(t\,(H_0 + H_1))\cdot p_0$$

$$= \sum_{k=0}^{\infty}\left[\int_0^t dt_k \int_0^{t_k} dt_{k-1}\cdots\int_0^{t_2} dt_1\, \exp((t-t_k)H_0)\,H_1\,\exp((t_k-t_{k-1})H_0)\cdots H_1\,\exp(t_1\,H_0)\cdot p_0\right]$$

[Annals of Math. and A. I., 47(3-4), January 2007]

Time Ordered Product Expansion (TOPE)

- Time Ordered Product Expansion (TOPE) formula:

$$\exp(t\,H)\cdot p_0 = \exp(t\,(H_0 + H_1))\cdot p_0$$

$$= \sum_{n=0}^{\infty}\left[\int_0^t d\,t_1 \int_{t_1}^t d\,t_2 \cdots \int_{t_{n-1}}^t d\,t_n \exp((t-t_n)\,H_0)\,H_1 \exp((t_n-t_{n-1})\,H_0)\cdots H_1 \exp(t_1\,H_0)\right]\cdot p_0$$

  - H_0 = the easy part (if only recursively)
  - Feynman diagrams result (QFT: Perturbation theory, Wick's theorem)
- Gillespie stochastic simulation algorithm
  - $H_0 = \mathrm{diag}(\mathbf{1}\cdot H')\,;\ H_1 = H'$
  - Mixed ODE/SSA algorithm (novel)
- Other possibilities:
  - Exploit analytic solutions
  - Multiscale
  - Operator splitting - higher order

A Key Step in Deriving SSA

- TOPE:

$$\exp(t\,H)\cdot p_0 = \exp(t\,(H_0 + H_1))\cdot p_0$$

$$= \sum_{n=0}^{\infty}\left[\int_0^t d\,t_1 \int_{t_1}^t d\,t_2 \cdots \int_{t_{n-1}}^t d\,t_n \exp((t-t_n)\,H_0)\,H_1 \exp((t_n - t_{n-1})\,H_0)\cdots H_1 \exp(t_1\,H_0)\right]\cdot p_0$$

- SSA:

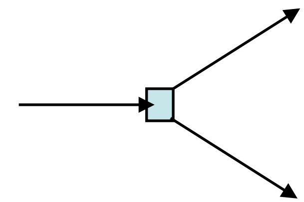
$$\Pr(\{n\},\,t\mid k) = \frac{\int_0^t d\,t_k \exp((t-t_k)\,H_0)\,H_1\cdot\Pr(\{n\},\,k-1\mid t_k)}{\int_0^{\infty} d\,t' \int_0^{t'} d\,t_k \exp((t'-t_k)\,H_0)\,H_1\cdot\Pr(\{n\},\,k-1\mid t_k)}$$

$$= \left[\hat{H}\cdot\Pr(\{n\},\,k-1\mid t_k)\right] / \left[\mathbf{1}\cdot\hat{H}\cdot\Pr(\{n\},\,k-1\mid t_k)\right]$$

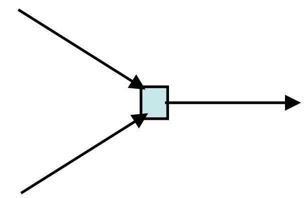
Elementary Processes

as "generalized reactions"

- $A(x) \rightarrow B(y) + C(z)$ **with** $\rho_f(x, y, z)$



- $B(y) + C(z) \rightarrow A(x)$ **with** $\rho_r(y, z, x)$



- Examples
  - Chemical reaction networks w/o params
  - $\text{HydrogenAtom}(x), \text{HydrogenAtom}(y) \rightarrow \text{HydrogenMolecule}(z)$
    $$\textbf{with } f(\| x-y \|) \exp\left(-\left(\| x-z \|^2 + \| y-z \|^2 \right) / 2\sigma^2 \right)$$
  - $\{bacterium(x),\ macrophage(y)\} \rightarrow macrophage(y)$ **with** $\rho(\|x-y\|)$

- Effective conservation laws
  - E.g. $\int N_A(x)\, dx + \int N_B(y)\, dy$,
    $\int N_A(x)\, dx + \int N_C(z)\, dz$

“Linguistic” ontology

Part of speech	Biology	Model syntax	Math. semantics
Nouns	Objects	Parameterized terms	Fock space
Verbs	Processes	Generalized reactions	Time-evolution operators
Prepositions	Relationships	OID params	Graphs

Basic Syntax for a Modeling Language: Stochastic Parameterized Grammars (SPG's)

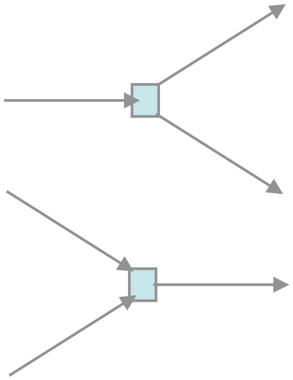
- Γ = set of rules
- Each rule has:
  - *LHS* $\rightarrow$ *RHS* {**keyword** *expression*}$_*$
  - Parameterized term instances within *LHS* and/or *RHS*
  - *LHS*, *RHS*: *multisets* (of such terms) with Variables
    - *LHS* matches subsets of parameterized term instances in the Pool
  - Keyword clauses specify probability rate, as a product
- Keyword: **with**
  - Algebraic sublanguage for probability rate functions
    - rates are independent of # of other matches; oblivious.

[Annals of Math. and A. I., 47(3-4), January 2007]

SSA for SPG's

- SSA derived from TOPE for "fresh events"
- Algorithm
  - Factor $\rho^{(r)}(x_{in}, x_{out}) = k^{(r)}(x_{in})\, p^{(r)}(x_{out} \mid x_{in})$
  - Compute SSA propsensities as $k^{(r)}(x_{in})$
  - Decide which reaction r to execute, as usual
  - Draw x_{out} from $p^{(r)}(x_{out} \mid x_{in})$ and execute
- Result: reaction schemata, or rewrite rules
  - Integration over parameters ~ pattern matching

A Modeling Language for Biological Development



- "Dynamical Grammars" formal language
- SPG + ODE's
- Implementation: "Plenum"
  [Mjolsness and Yosiphon 2006]
- Generalizes Cellerator to multiscale dynamics
- Mixed stochastic/DAE simulation algorithms
- 1-page reimplementation of weak spring tissue model with cell division

[Annals of Math. and A. I., 47(3-4), January 2007]

SSA + ODEs

- SSA:

$$\mathcal{W}(I, t' \mid J, t) \approx \hat{W}_{I,J} \exp(-(t' - t) D_{JJ}) \mathbf{1}(t' \geqslant t)$$

- What if *D* varies with time?
  - $D\,\Delta t \rightarrow \int D(t)\,dt$
  - Achieve this with an extra ODE
- Heterogeneous dynamics simulation

Key Steps in Deriving Hybrid ODE/Discrete Event Simulation

- Using perturbation theory

$$\exp(t\,(-v(\{z\})\cdot\nabla_z - D)) = \exp(-t\,v(\{z\})\cdot\nabla_z)\exp\left(-\int_0^t dt'\,D(z(t'))\right)$$

$$= \exp(t\,O_{\{\mathrm{DE}\}})\exp\left(-\int_0^t dt'\,D\left(z(0)+\int_0^{t'} v(\{z\})\,dt''\right)\right)$$

- But this can also be achieved with ODE's:

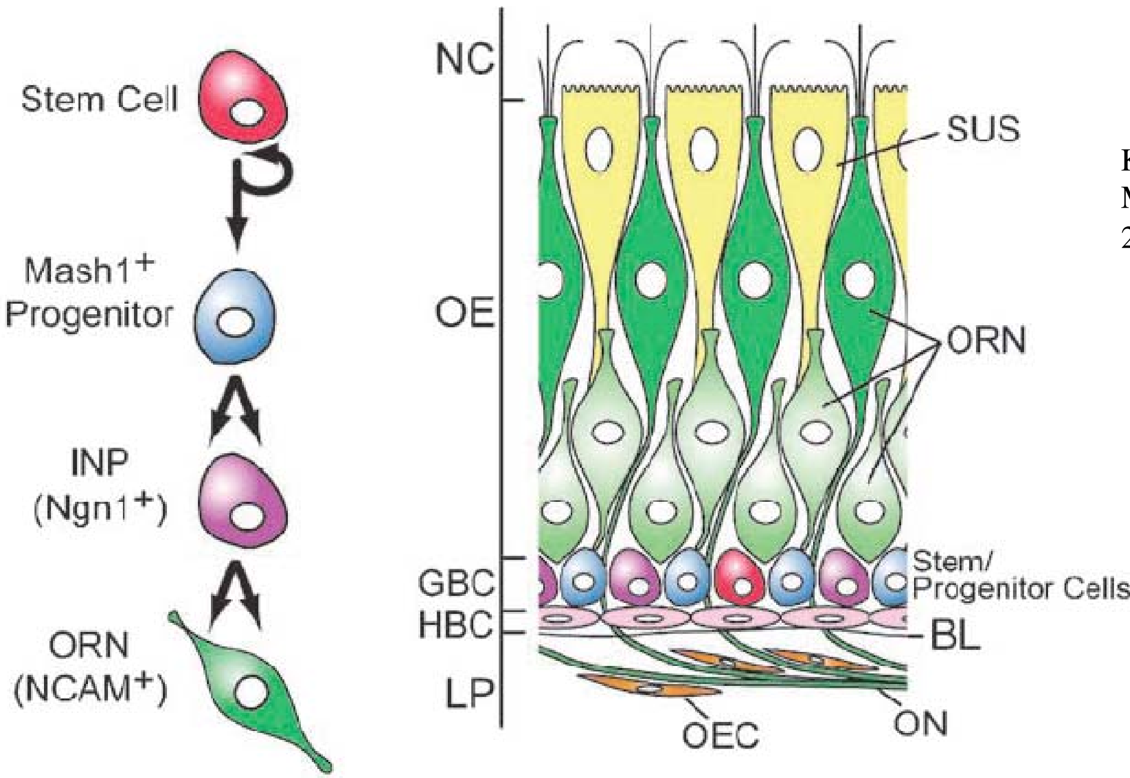
$$Z = (z,\,\lambda)$$
$$V(z) = (v(\{z\}),\,-D(z))$$
$$\nabla_Z = (\nabla_z,\,\partial_\lambda)$$
$$\boxed{\tilde{O}_{\{\mathrm{DE}\}} = V(Z)\,\nabla_Z = v(\{z\})\cdot\nabla_z - D(z)\,\partial_\lambda}$$

Plenum capabilities

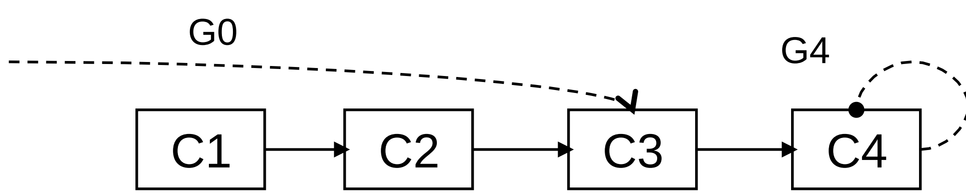
- Stochastic event + ODE models
- Variable-structure systems (VSS)
  - Processes that generate processes & compartments
  - Hybrid systems with change of dimensionality
- Graph grammars (GG)

  => dynamic geometries
- Limited multigrid diffusion (PDE) support

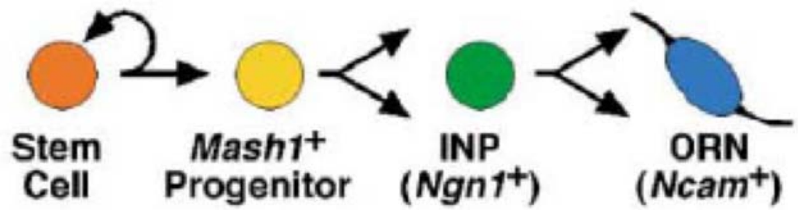
Example
Olfactory Receptor Lineage



Kawauchi, Beites, Crocker,Wu, Bonnin, Murray. Calof, Dev. Neuroscience 2004; 26:166–180



Concrete OE grammar



*(*stem cell mitosis*)*

$Stem::Cell\,(x,\ r) \rightarrow \{Stem::Cell\,(x_1,\ r/2^{1/d}),\ Stem::Cell\,(x_2, r/2^{1/d})\}, \quad \textbf{with}\ \ \rho_{0,1}\, P(x_1, x_2 \mid x)/T$

$Stem::Cell\,(x,\ r) \rightarrow \{Mash1::Cell\,(x_1, r/2^{1/d}),\ Mash1::Cell\,(x_2, r/2^{1/d})\}, \textbf{with}\ \ \rho_{0,2}\, P(x_1, x_2 \mid x)/T$

$Stem::Cell\,(x,\ r) \rightarrow \{Stem::Cell\,(x_1, r/2^{1/d}),\ Mash1::Cell\,(x_2, r/2^{1/d})\}, \quad \textbf{with}\ \ \rho_{0,3}\, P(x_1, x_2 \mid x)/T$

*(*Mash1 mitosis*)*

$Mash1::Cell\,(x,\ r) \rightarrow \{Mash1::Cell\,(x_1, r/2^{1/d}),\ Mash1::Cell\,(x_2, r/2^{1/d})\}, \textbf{with}\ \ \rho_{1,1}\, P(x_1, x_2 \mid x)/T$

$Mash1::Cell\,(x,\ r) \rightarrow \ \{INP::Cell\,(x_1, r/2^{1/d}),\ INP::Cell\,(x_2, r/2^{1/d})\}, \quad \textbf{with}\ \ \rho_{1,2}\, P(x_1, x_2 \mid x)/T$

*(*INP mitosis*)*

$\{INP::Cell\,(x, r),\ g = Signal\_Field\ (\phi)\} \rightarrow \{INP::Cell\,(x_1, r/2^{1/d}),\ INP::Cell\,(x_2, r/2^{1/d}),\ g\}$

$\quad \textbf{with}\ \ \rho_{2,1}(\phi(x))\, P(x_1, x_2 \mid x)/T$

$\{INP::Cell\,(x, r),\ g = Signal\_Field\ (\phi)\} \rightarrow \{ORN::Cell\,(x_1, r/2^{1/d}),\ ORN::Cell\,(x_2, r/2^{1/d}),\ g\}$

$\quad \textbf{with}\ \ \rho_{2,2}(\phi(x))\, P(x_1, x_2 \mid x)/T$

*(*cell growth*)*

$Cell(x, r) \rightarrow Cell(x, r)$

$\quad \textbf{solving}\ \left\{ \frac{dr}{dt} = v(r) \right\}$

*(*cell movement due to neighbor cell position*)*

$\{\mathrm{c1} = Cell(x_1, r_1),\ \mathrm{c2} = Cell(x_2, r_2)\} \rightarrow \{\mathrm{c1},\ \mathrm{c2}\}$

$\quad \textbf{solving}\ \left\{ \frac{dx_1}{dt} = \varphi(x_1, r_1, x_2, r_2) \right\}$

*(*cell movement due to boundary position*)*

$\{\mathrm{c1} = Cell(x_1, r_1),\ b = Boundary(x_2)\} \rightarrow \{\mathrm{c1},\ b\}$

$\quad \textbf{solving}\ \left\{ \frac{dx_1}{dt} = \varphi(x_1, r_1, x_2, 0) \right\}$

Epithelial Grammar

grammar Epithelial[

(*replication*)

$\mathrm{Cell}(\tau, x, r, g) \to \{\mathrm{Cell}(\tau, x - r/2, r/2, g), \mathrm{Cell}(\tau, x + r/2, r/2, g)\}$

with $\rho_1(\tau, r, g)$

(*differentation*)

$\mathrm{Cell}(\tau, x, r, g) \to \{\mathrm{Cell}(\tau + 1, x - r/2, r/2, g), \mathrm{Cell}(\tau + 1, x + r/2, r/2, g)\}$

with $\rho_2(\tau, r, g)$

(*death*)

$\mathrm{Cell}(\tau, x, r, g) \to \{\,\}$

with $\rho_3(\tau, r, g)$

(*growth*)

$\mathrm{Cell}(\tau, x, r, g) \to \mathrm{Cell}(\tau, x, r, g)$

solving $\left\{\frac{dr}{dt} = k\right\}$

(*motion*)

$\{\mathrm{Cell}(\tau_1, x_1, r_1, g_1), \mathrm{Cell}(\tau_2, x_2, r_2, g_2)\} \to \{\mathrm{Cell}(\tau_1, x_1, r_1, g_1), \mathrm{Cell}(\tau_2, x_2, r_2, g_2)\}$

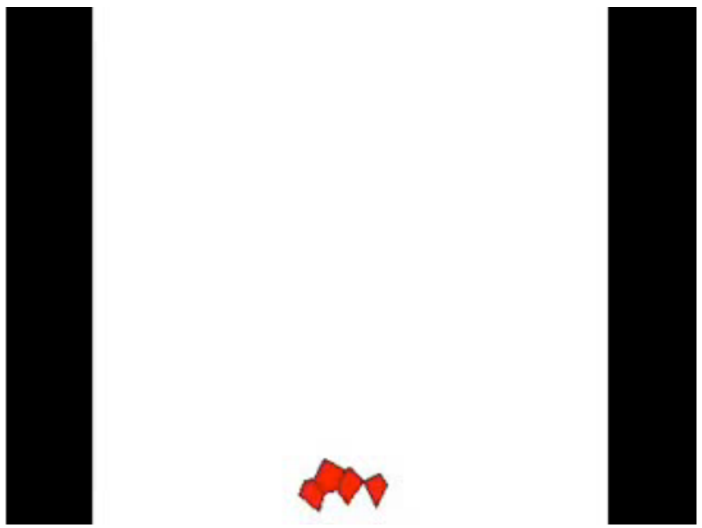
solving $\left\{\frac{dx_1}{dt} = m(x_1, r_1, x_2, r_2)\right\}$

(*protein concentration*)

$\{\mathrm{Cell}(\tau_1, x_1, r_1, g_1), \mathrm{Cell}(\tau_2 = 4, x_2, r_2, g_2)\} \to \{\mathrm{Cell}(\tau_1, x_1, r_1, g_1), \mathrm{Cell}(\tau_2 = 4, x_2, r_2, g_2)\}$

solving $\{g_1 = f(x_1, x_2, r_2)\}$

]



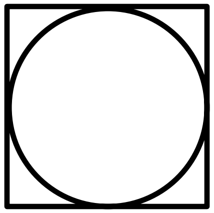
Some URLs

- Cellerator, xCellerator, Cellzilla
  - www.xcellerator.info
  - www.cellerator.org
- Sigmoid
  - www.sigmoid.org
- Plenum
  - http://computableplant.ics.uci.edu/~guy/PlenumLicense.html

Methods

- Operator algebra
- Time-Ordered Product Expansion
- Rejection sampling

Rejection Sampling



Rejection sampling allows one to exploit probability bounds in exact sampling, as follows: given a target distribution $P(x)$ and an algorithm for sampling from a related distribution $P'(x)$ and from the uniform distribution $U(u)$ on [0,1], and if

$$P(x) < M\,P'(x)$$

for some constant $M > 1$, then $P(x)$ satisfies

$$P(x) = P'(x)\,\frac{P(x)}{M\,P'(x)} + (1 - 1/M)\,P(x)$$

and therefore also

$$P(x) = \int P'(x')\,dx' \int U(u)\,du \left[\mathbf{1}\left(u < \frac{P(x')}{M\,P'(x')}\right)\cdot\delta(x - x') + \mathbf{1}\left(u \geqslant \frac{P(x')}{M\,P'(x')}\right)\cdot P(x)\right]$$

which constitutes a mixture distribution, that can be applied recursively as needed to sample from $P(x)$. Pseudocode for sampling $P(x)$ according to Equation 13 is as follows (where "//" introduces a comment):

while not accepted {

sample $P'(x)$ and $U(u)$; // $P'(x)$ only approximates $P(x)$

compute Accept(x) = $P(x)/(M\,P'(x))$; // acceptance probability

if $u <$ Accept(x) **then** accept x;

} // now $P(x)$ is sampled exactly

Stochastic Simulation

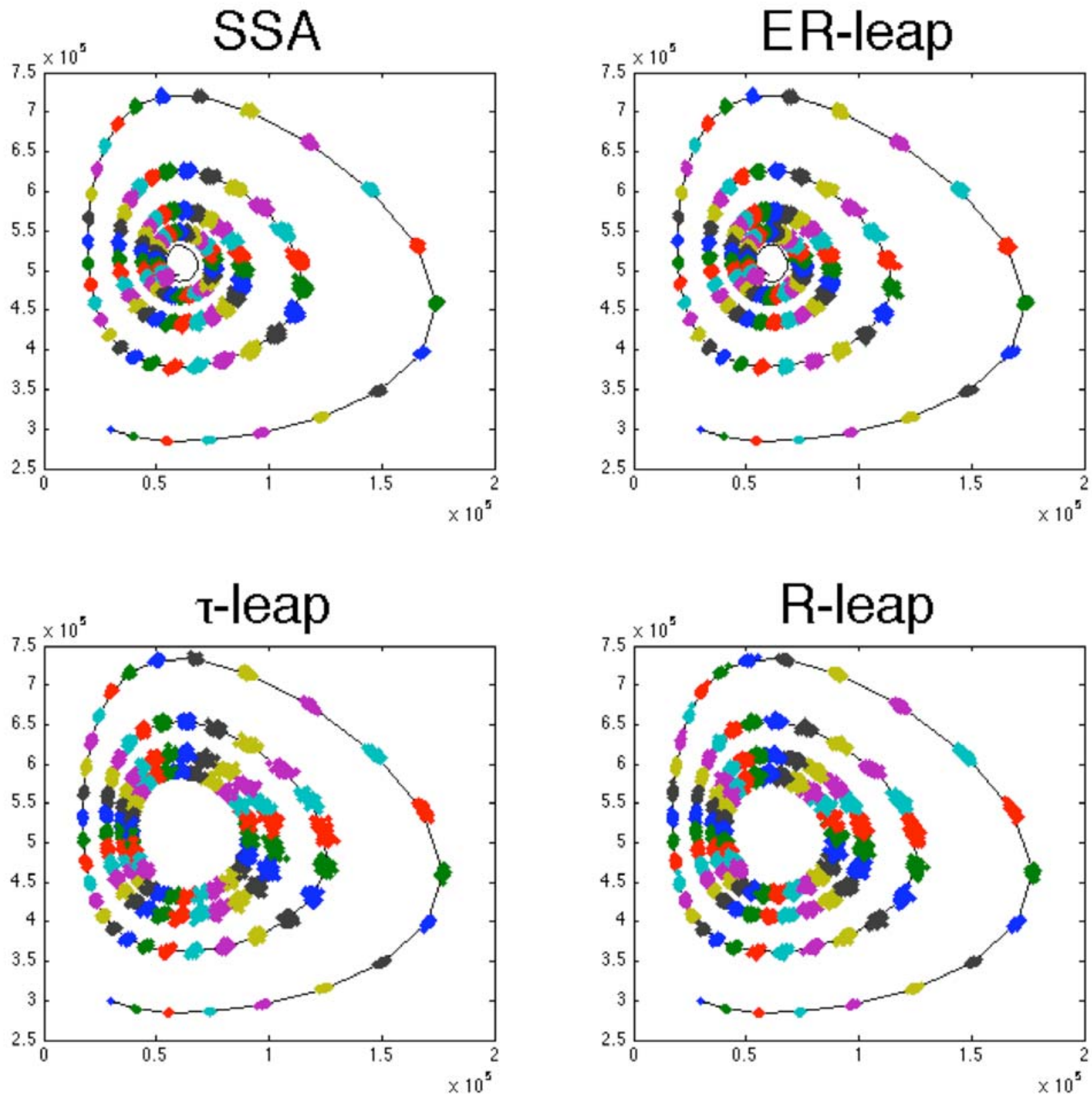
- SSA: $\mathcal{W}(I, t' \mid J, t) \approx \hat{W}_{I,J} \exp(-(t'-t) D_{J\,J})\, \mathbf{1}\,(t' \geqslant t)$

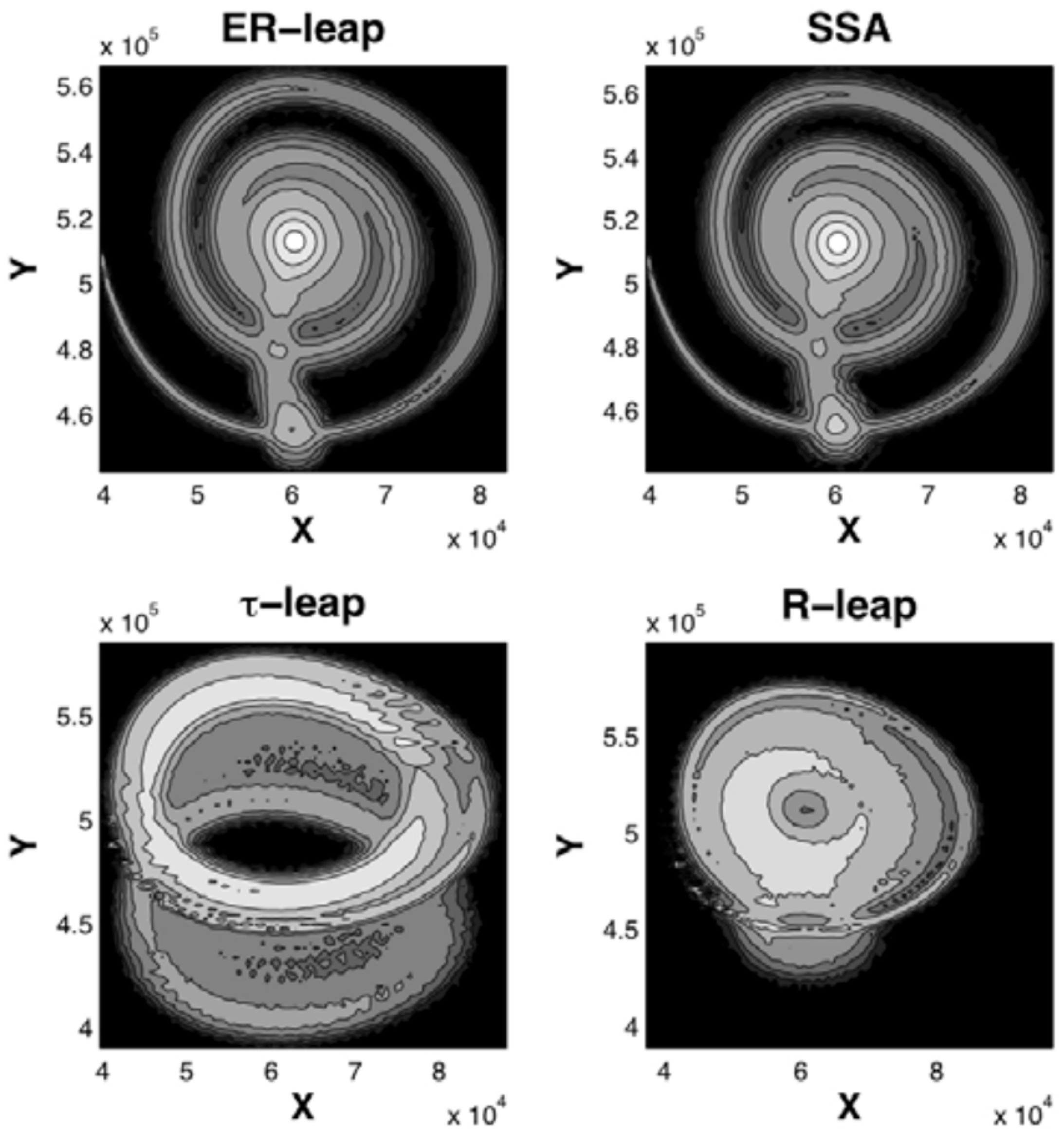
$$\Pr(.\mid J, k) = \mathcal{W}^k \circ \Pr(.\mid J, 0) = \left[\hat{W} \exp(-\Delta\, t\, D)\, \mathbf{1}\,(\Delta\, t \geqslant 0)\right]^k \circ \Pr(.\mid J, 0)$$

- Exact R-leap:

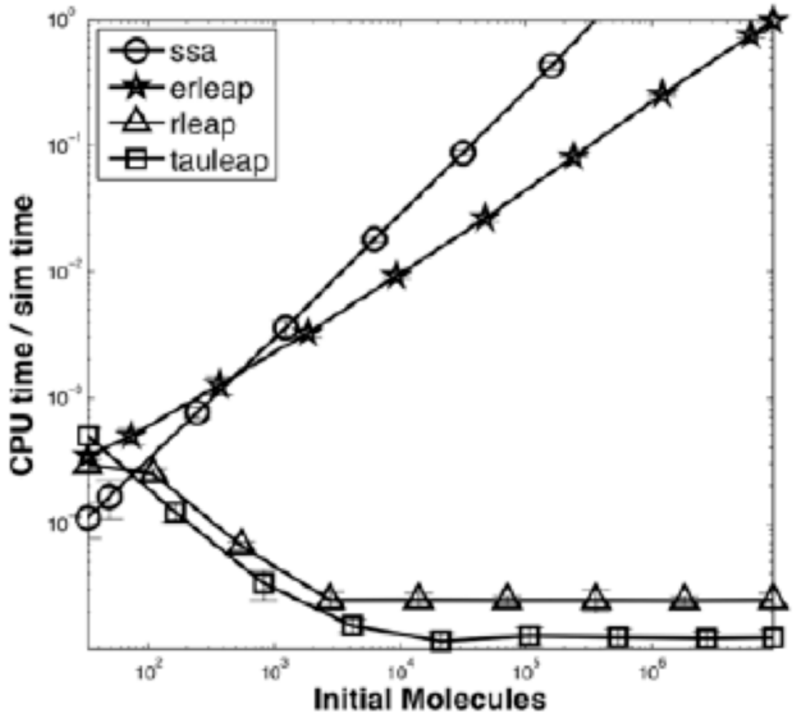
$$\left[\prod_{k=L-1 \searrow 0} \hat{W}\ \exp\left(-\tau_k\, D\right)\right]_{I_L, I_0} = \frac{\left(\tilde{D}_{I_0\, L-1}\right)^L}{\left(\underset{\sim}{D}_{I_0\, L-1}\right)^L} \sum_{\{s \mid s_r \in \mathbb{N},\, \sum_r s_r = L\}} \text{Multinomial}(\boldsymbol{s} \mid \boldsymbol{p}, L)$$

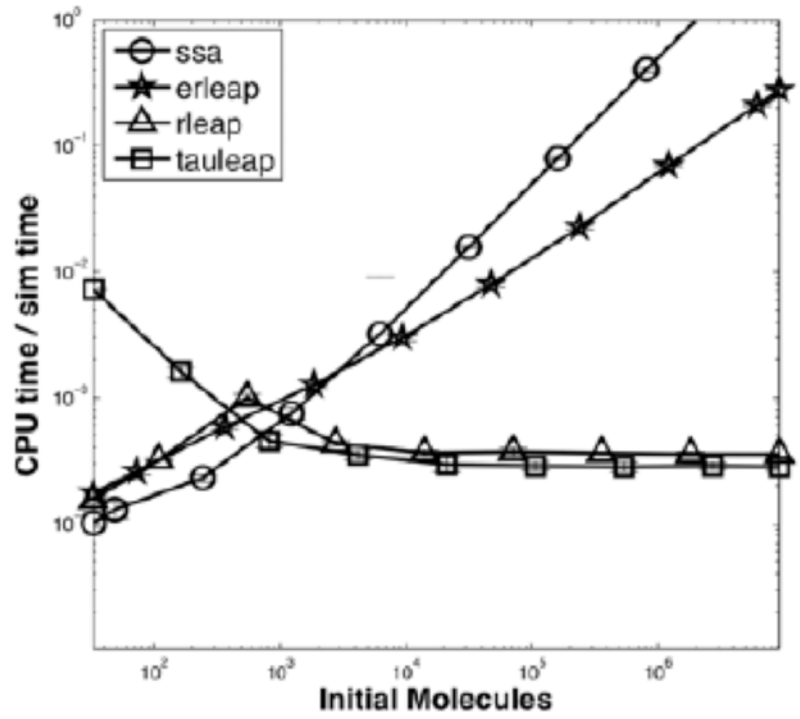
$$\times \text{Erlang}\left(\sum_k \tau_k \,\middle|\, L, \underset{\sim}{D}_{I_0\, L-1}\right) \text{UniformSimplex}(\boldsymbol{\tau}; L)\, \text{Accept}(\boldsymbol{s}, L, \boldsymbol{\tau})$$


SSA
ER-leap
τ-leap
R-leap
x 10^5
7.5
7
6.5
6
5.5
5
4.5
4
3.5
3
2.5
0
0.5
1
1.5
2
x 10^5


ER–leap
x 10^5
5.6
5.4
5.2
5
4.8
4.6
Y
4
5
6
7
8
X
x 10^4
SSA
x 10^5
5.6
5.4
5.2
5
4.8
4.6
Y
4
5
6
7
8
X
x 10^4
τ–leap
x 10^5
5.5
5
4.5
4
Y
4
5
6
7
8
X
x 10^4
R–leap
x 10^5
5.5
5
4.5
4
Y
4
6
8
X
x 10^4

Simulation speed



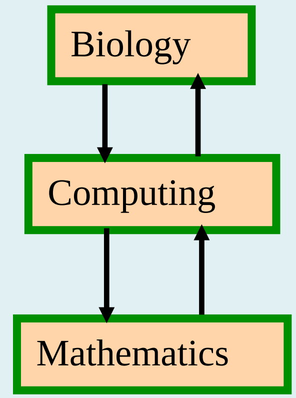


Methods

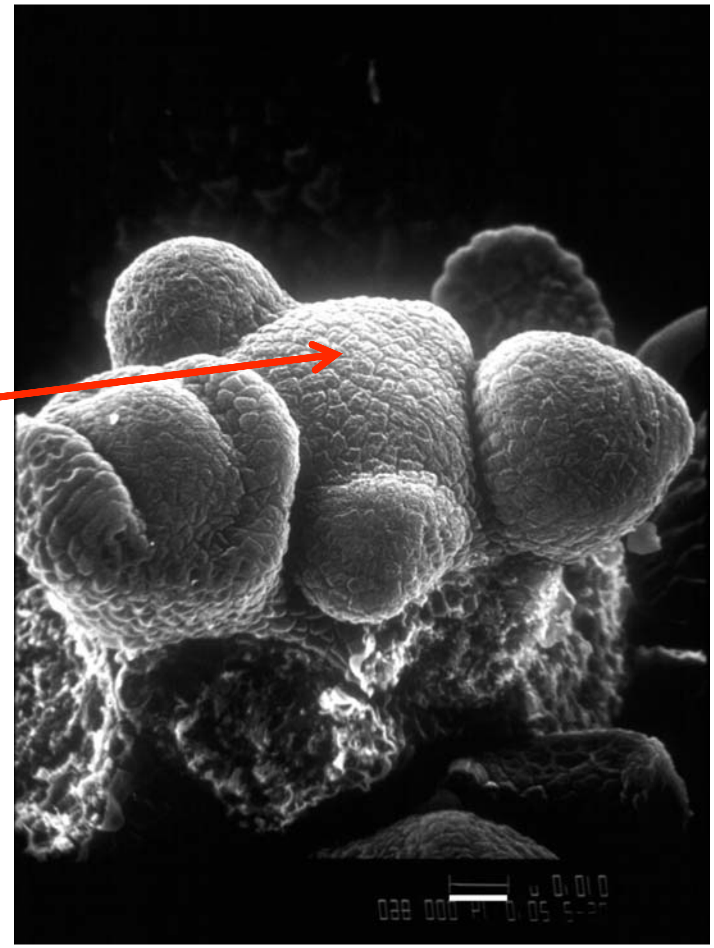
- Operator algebra
- Time-ordered Product Expansion
- Rejection sampling

Outline: Math. Methods

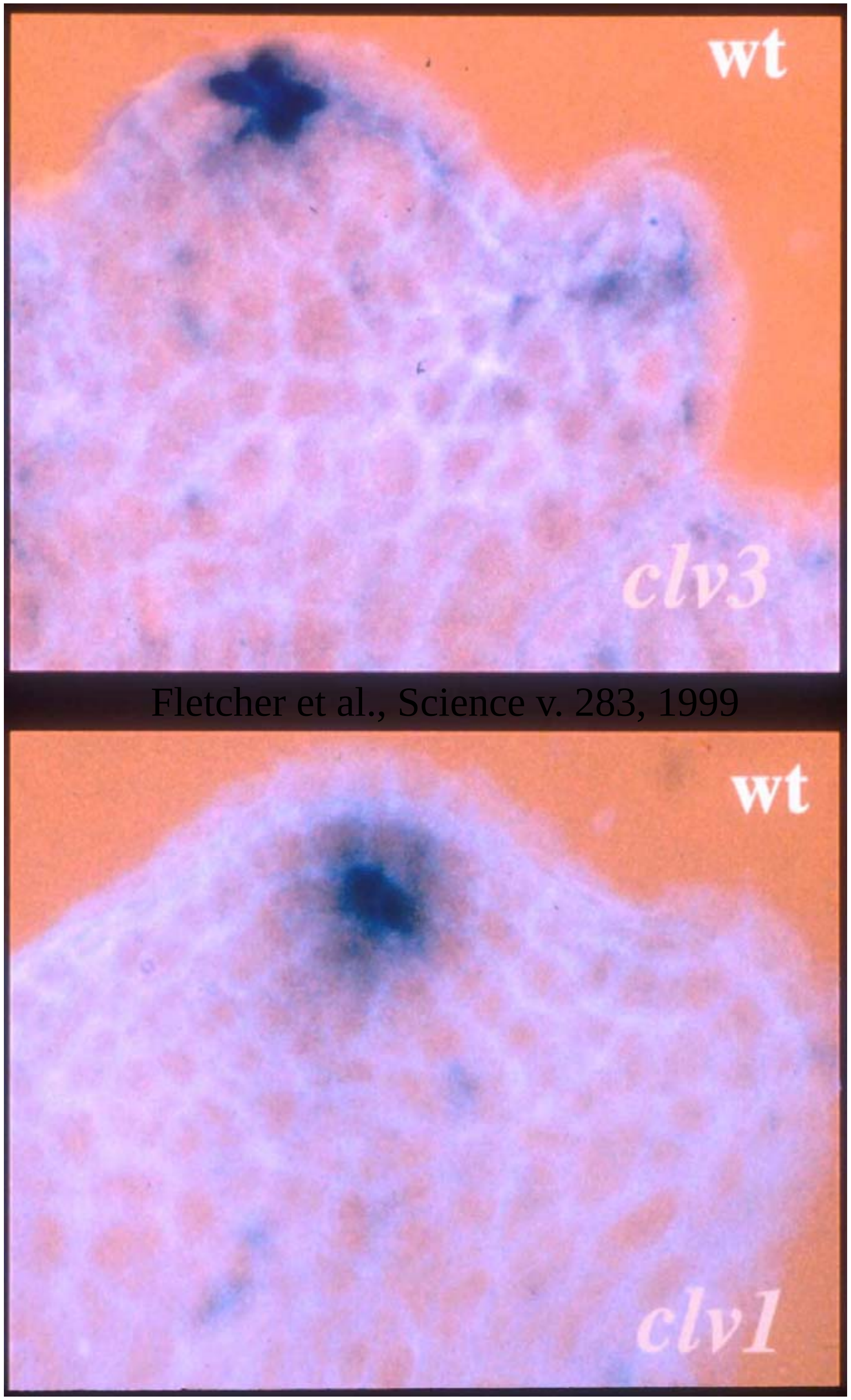
- Statistical Mechanics
  - SM in metabolism, transcription
- Stochastic Dynamics
  - Operator algebra
- Classical Spatial Dynamics
  - Hybrid systems; elastic dynamics
- Computational Dynamics
  - Semantics
  - Computational Morphodynamics



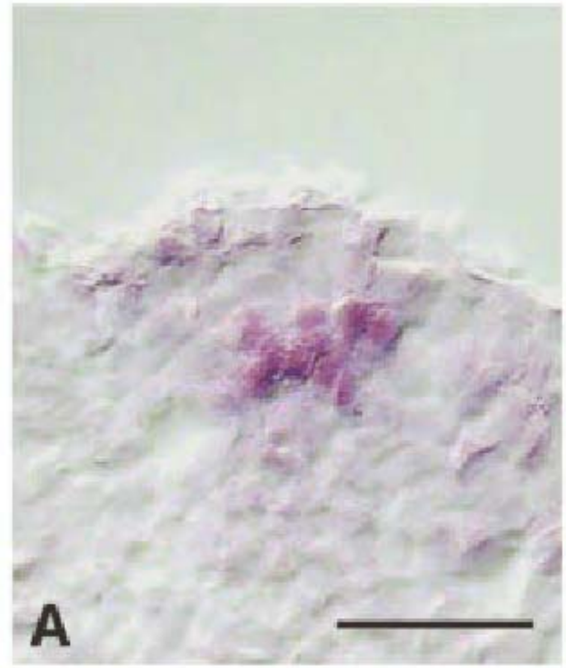
Arabidopsis
Shoot Apical Meristem (SAM)



WILD TYPE | *clavata3* mutant

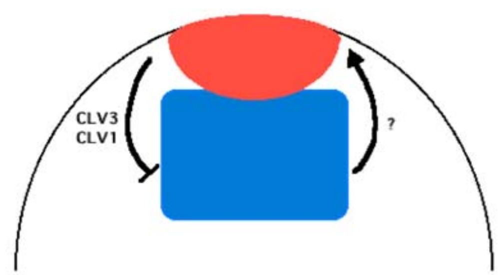


Fletcher et al., Science v. 283, 1999

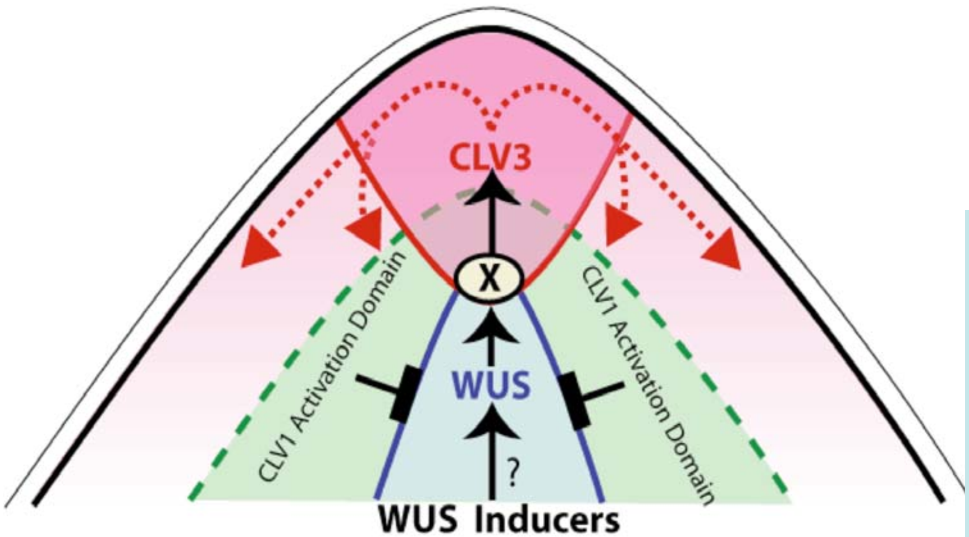


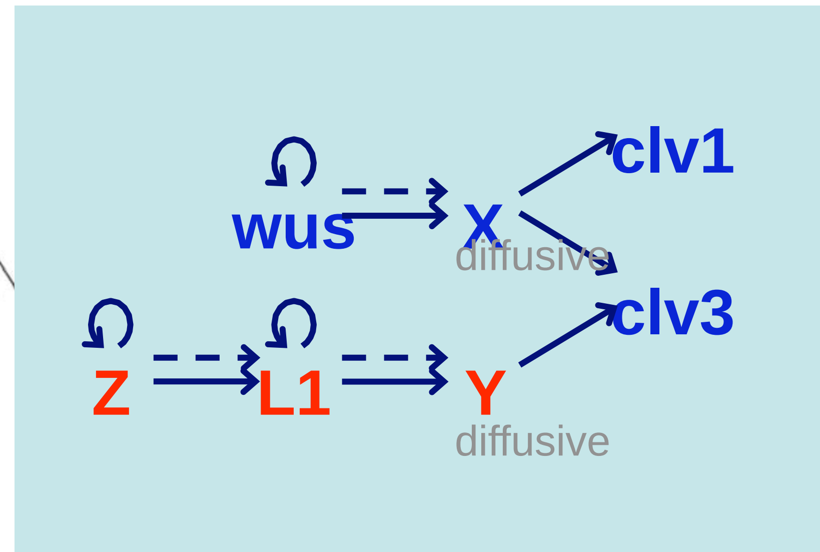
WUS

Brand et. al., Science **289**, 617-619, (2000)



CLV3/WUS networks

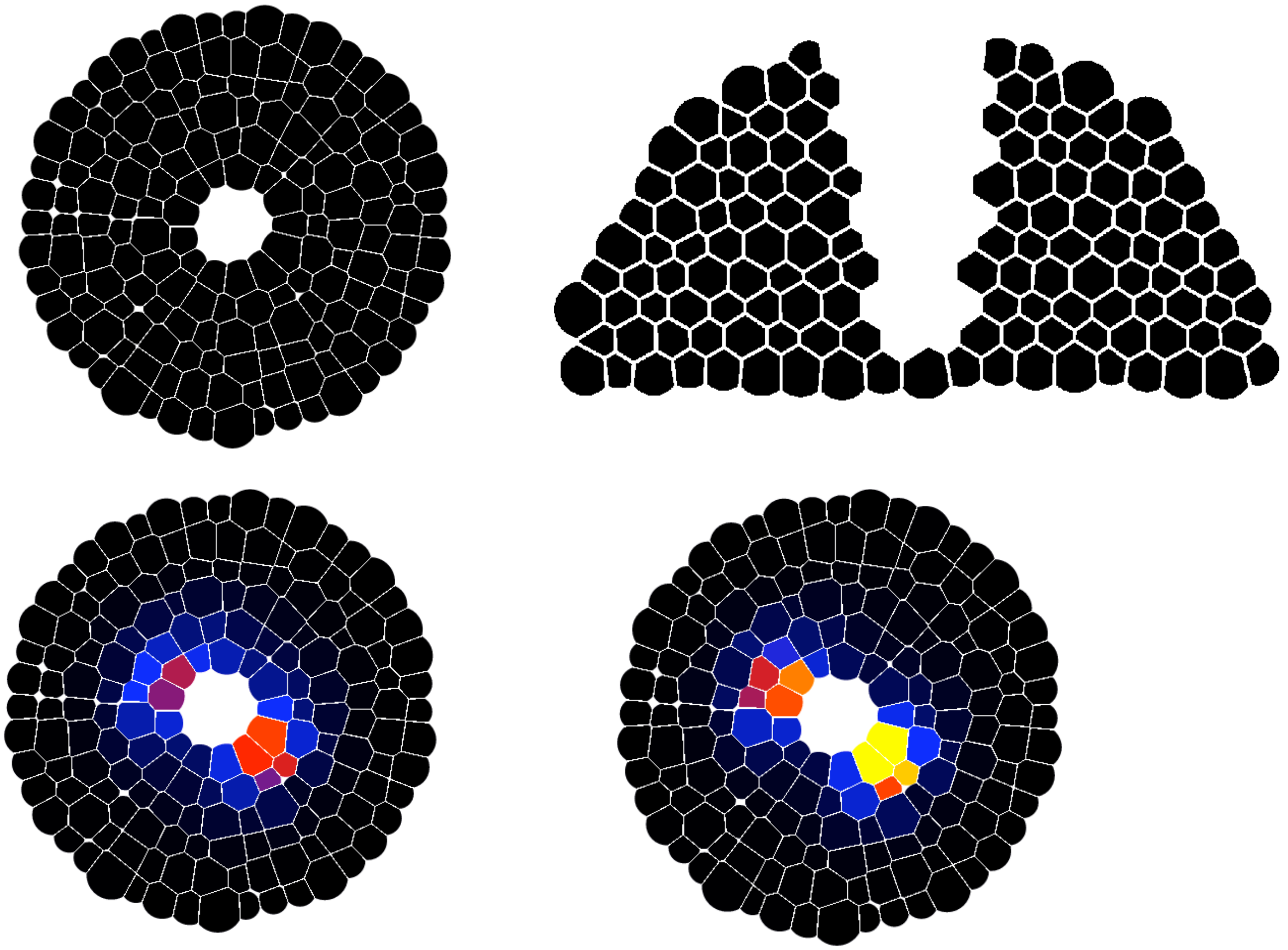




$$
\begin{aligned}
&\{\{\mathrm{CLV1} + \mathrm{CLV3} \rightleftharpoons \mathrm{CLV1Active},\ \mathrm{a1},\ \mathrm{d1}\},\\
&\{X \mapsto \mathrm{CLV1},\ \mathrm{GRN}[\mathrm{hGRN} \to \mathrm{h2},\ \mathrm{RGRN} \to \mathrm{v2},\ \mathrm{nGRN} \to \mathrm{n2}]\},\\
&\{\mathrm{WUS} \mapsto X,\ \mathrm{GRN}[\mathrm{hGRN} \to \mathrm{h3},\ \mathrm{RGRN} \to \mathrm{v3},\ \mathrm{nGRN} \to \mathrm{n3}]\},\\
&\{\mathrm{WUSI} \mapsto \mathrm{WUS},\ \mathrm{GRN}[\mathrm{hGRN} \to \mathrm{h4},\ \mathrm{RGRN} \to \mathrm{v4},\ \mathrm{nGRN} \to \mathrm{n4}]\},\\
&\left\{ Z \overset{\mathrm{CLV1Active}}{\Longrightarrow} \mathrm{Z1},\ \mathrm{MM}[\mathrm{K5},\ \mathrm{v5}] \right\},\\
&\{\mathrm{Z1} + \mathrm{WUSI} \rightleftharpoons Y,\ \mathrm{a6},\ \mathrm{d6}\}\}
\end{aligned}
$$

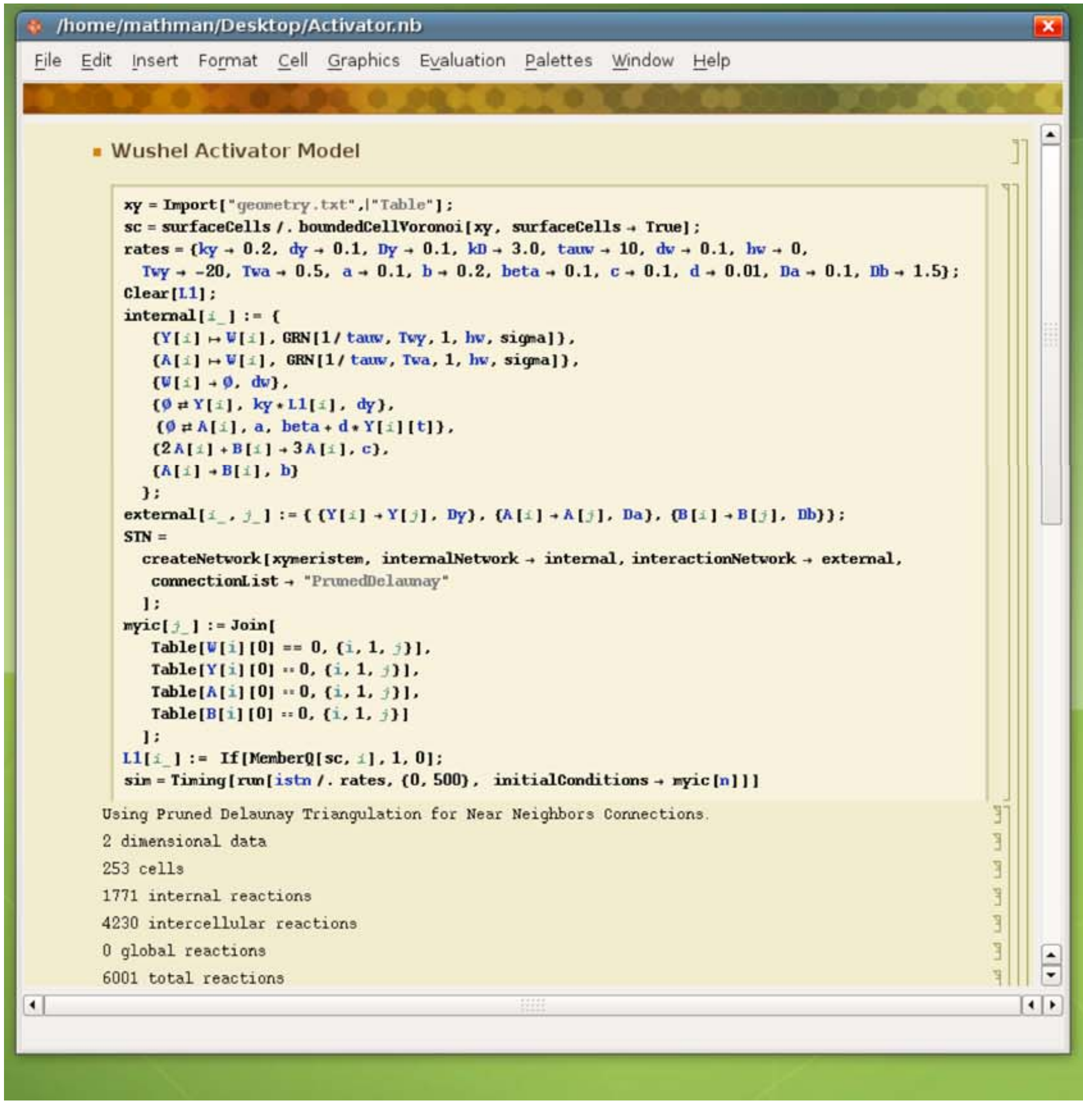
Jönsson et al., Bioinformatics 21, 2005

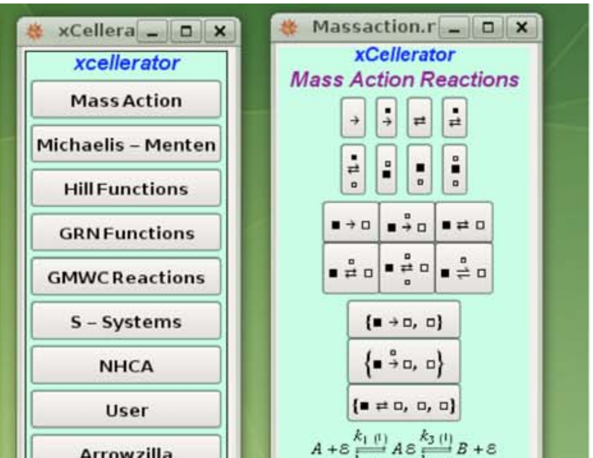
Laser ablation simulation (2D)

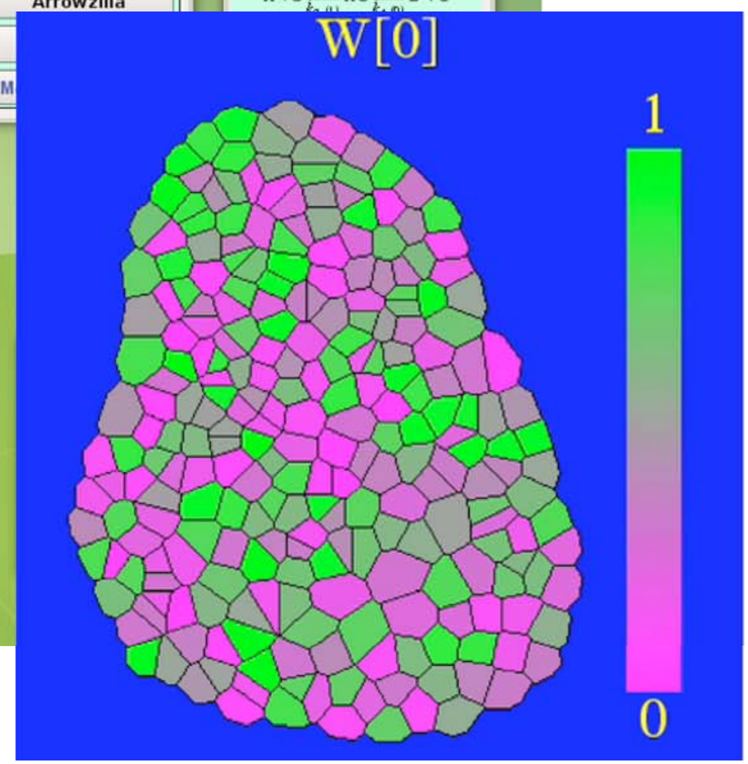


Jönsson et al., Bioinformatics 21, 2005

Cellzilla WUS model

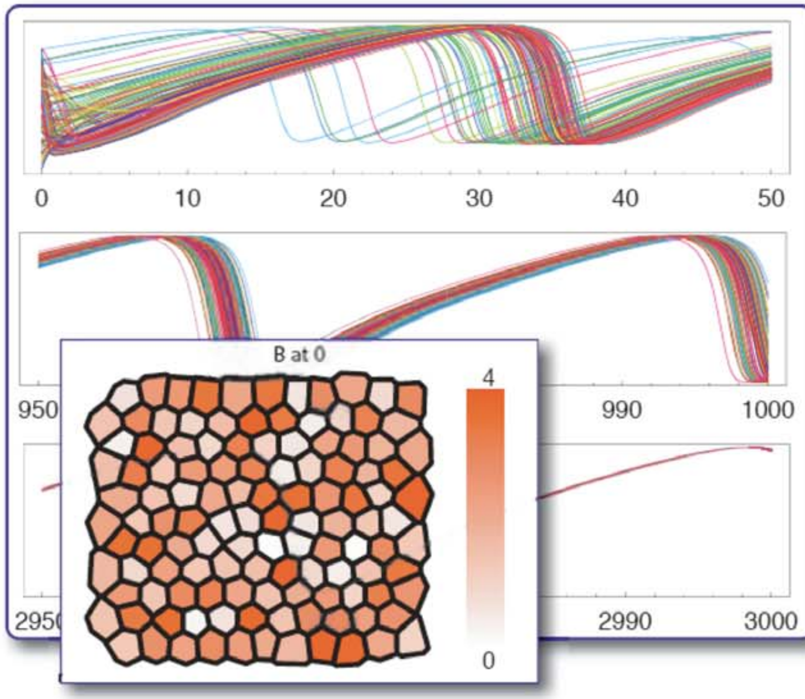






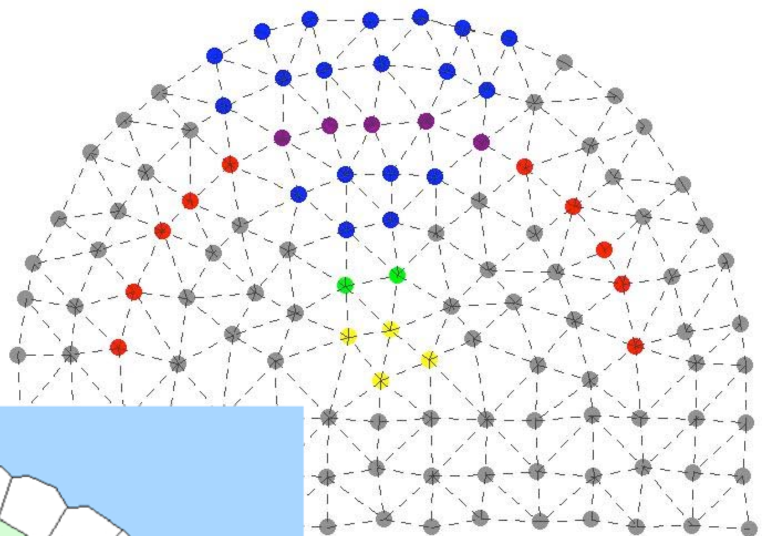
Cellzilla Brusselator

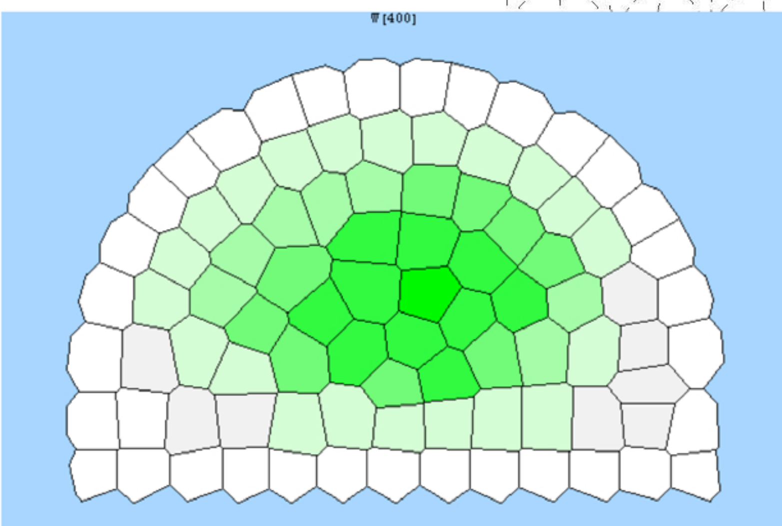
```
(* Define the Grid *)
xy = rectGrid[10, 10, 1];

(* Define the reaction network *)
n = Length[xy]; internal[i_] := {{Ø ⇄ A[i], k1, k2},
  {2 A[i] + B[i] → 3 A[i], k3}, {A[i] → B[i], k4}};
external[i_, j_] := { {A[i] → A[j], DA}, {B[i] → B[j], DB}};

(* Generate the entire sytem of reactions *)
STN = createNetwork[xy, internalNetwork → internal,
   interactionNetwork → external];

(* Generate the differential equations *)
istn = interpret[STN];

(* Define random initial conditions *)
r := Random[Real, {0, 4}];
ic = Table[{A[i][0] == r, B[i][0] == r}, {i, 1, n}] // Flatten;

(* Define the rate constants *)
rates = {k1 → .2, k2 → .2, k3 → .2, k4 → .6, DA → 0.002, DB → 0.

(* Run a simulation *)
sim = run[istn /. rates, {0, 3000}, initialConditions → ic,
    MaxSteps → 100000];
```



B. Shapiro et al., ICSB 2007

CLV/WUS model behavior





Activation domains in Cellerator model: WUS (yellow), CLV3I1 (green), CLV3 (blue and purple), CLV1 (red and purple).

Methods

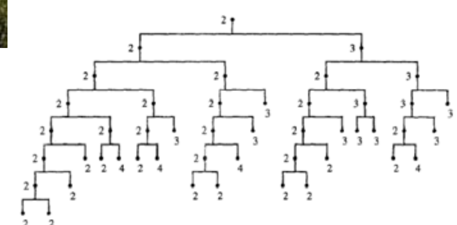
- Hybrid systems
- Homotopy methods
- Finite element methods

A multiscale question

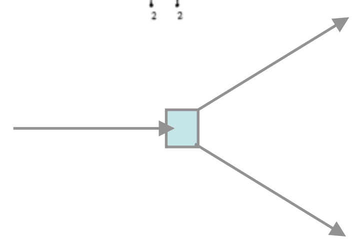
for Variable-Structure Systems:

Where does “branching” come from?

- – Trees branch

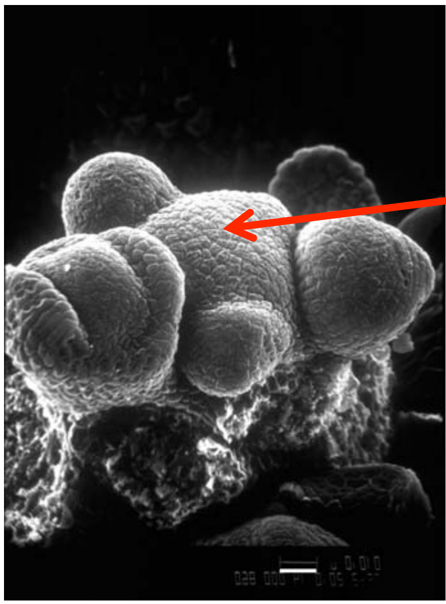


- – Cell lineages branch

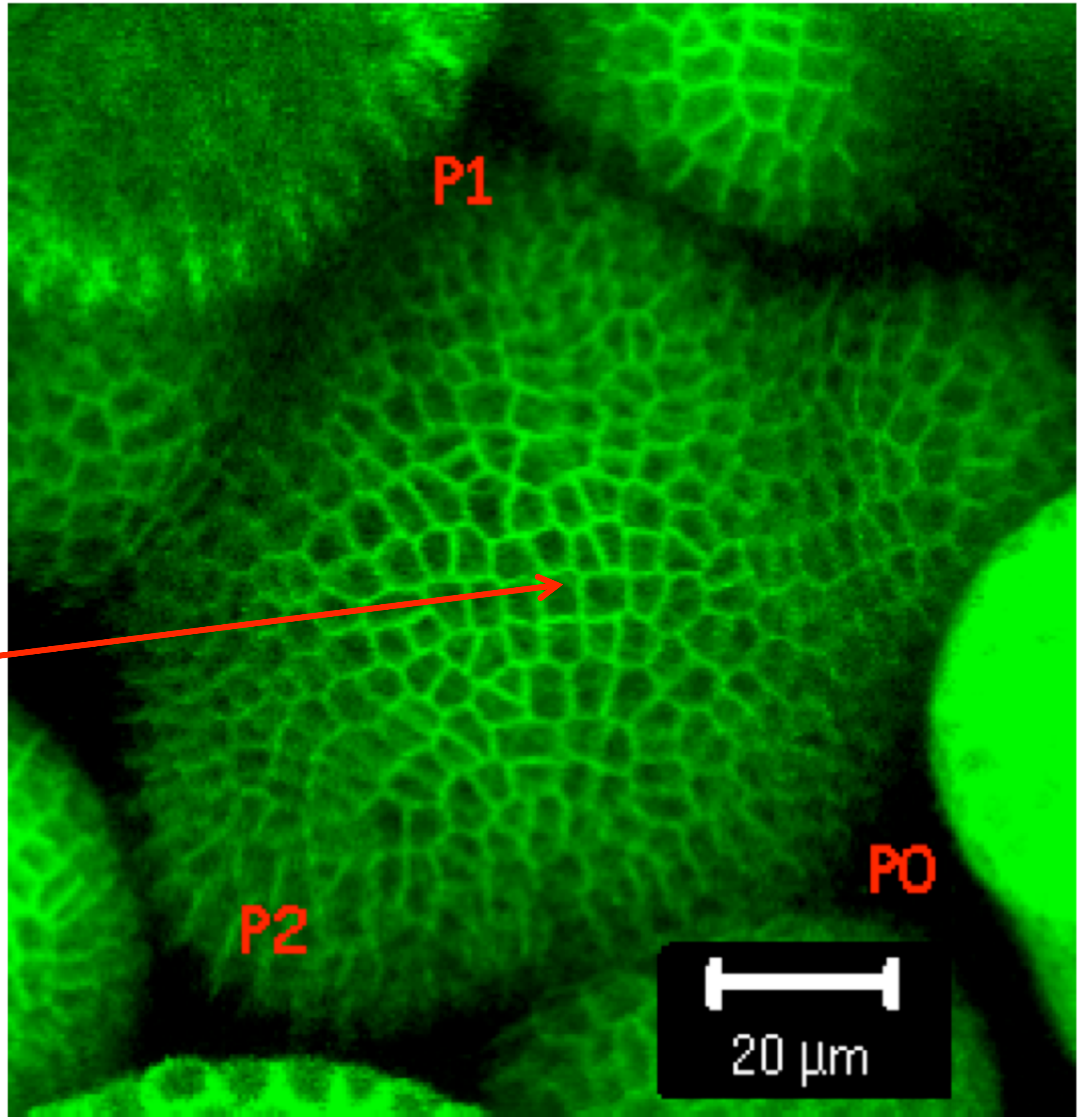


- – Chemical reactions branch
- – Is there a relationship?

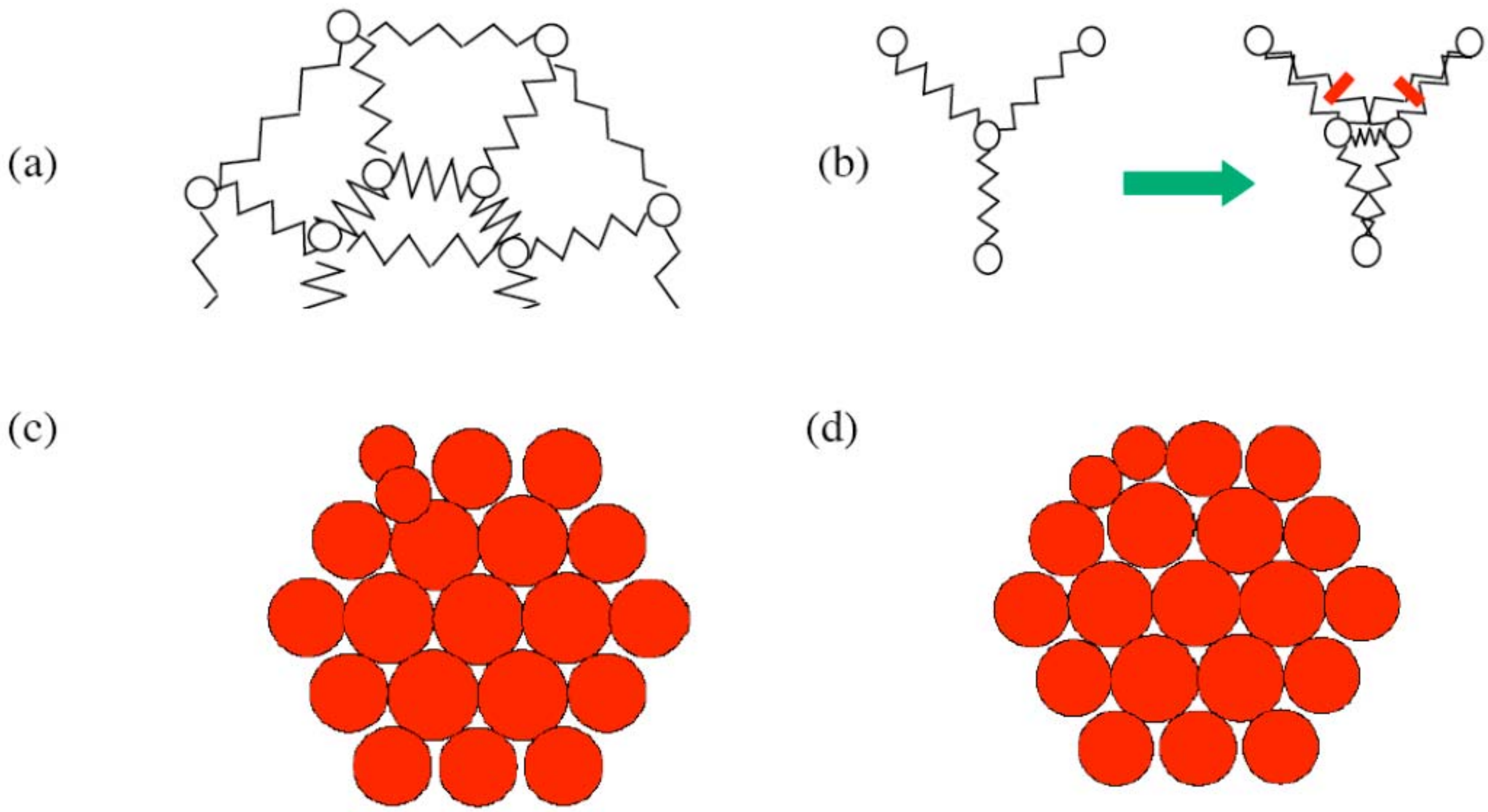
SAM growth imagery PIN1 cell walls



Venu Reddy, Caltech



Weak spring model



[J. Plant Growth Regulation, 25(4), 270-277, December 2006]

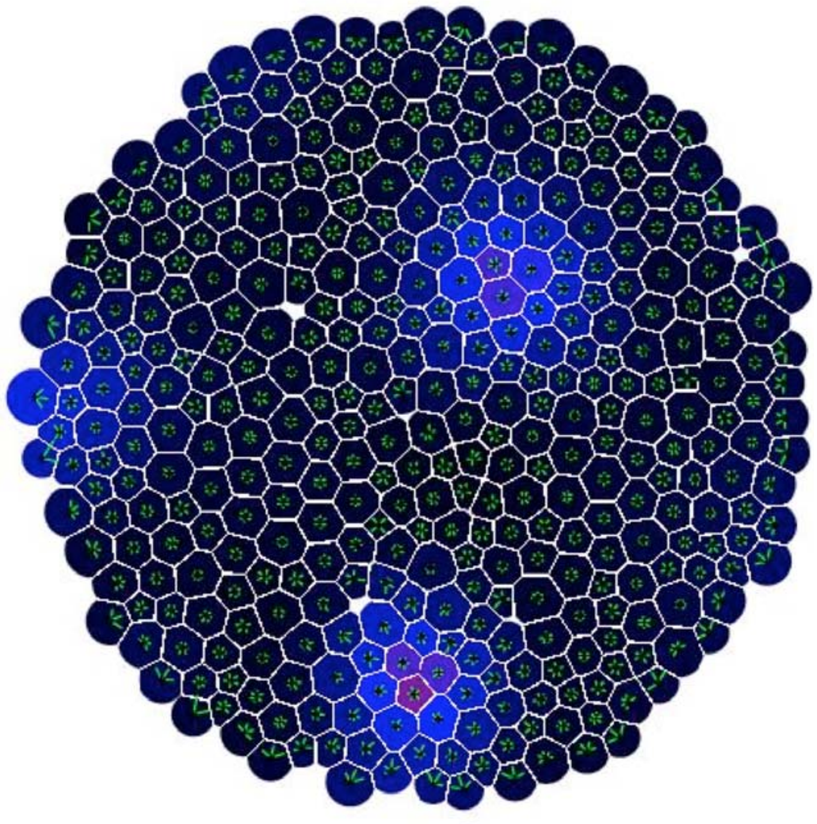
Variable-Structure (Dynamical) Systems

- Definition:

  Dynamical systems in which the number of state-bearing objects and/or their relationships change over time.

- Examples:
  - gene duplication in a GRN
  - dynamical regulatory networks
  - dynamic spatial compartments in developmental biology, geology, …

Multiscale dynamic model of phyllotaxis



Emergence of new extended, interacting *objects*: floral meristem primordia.

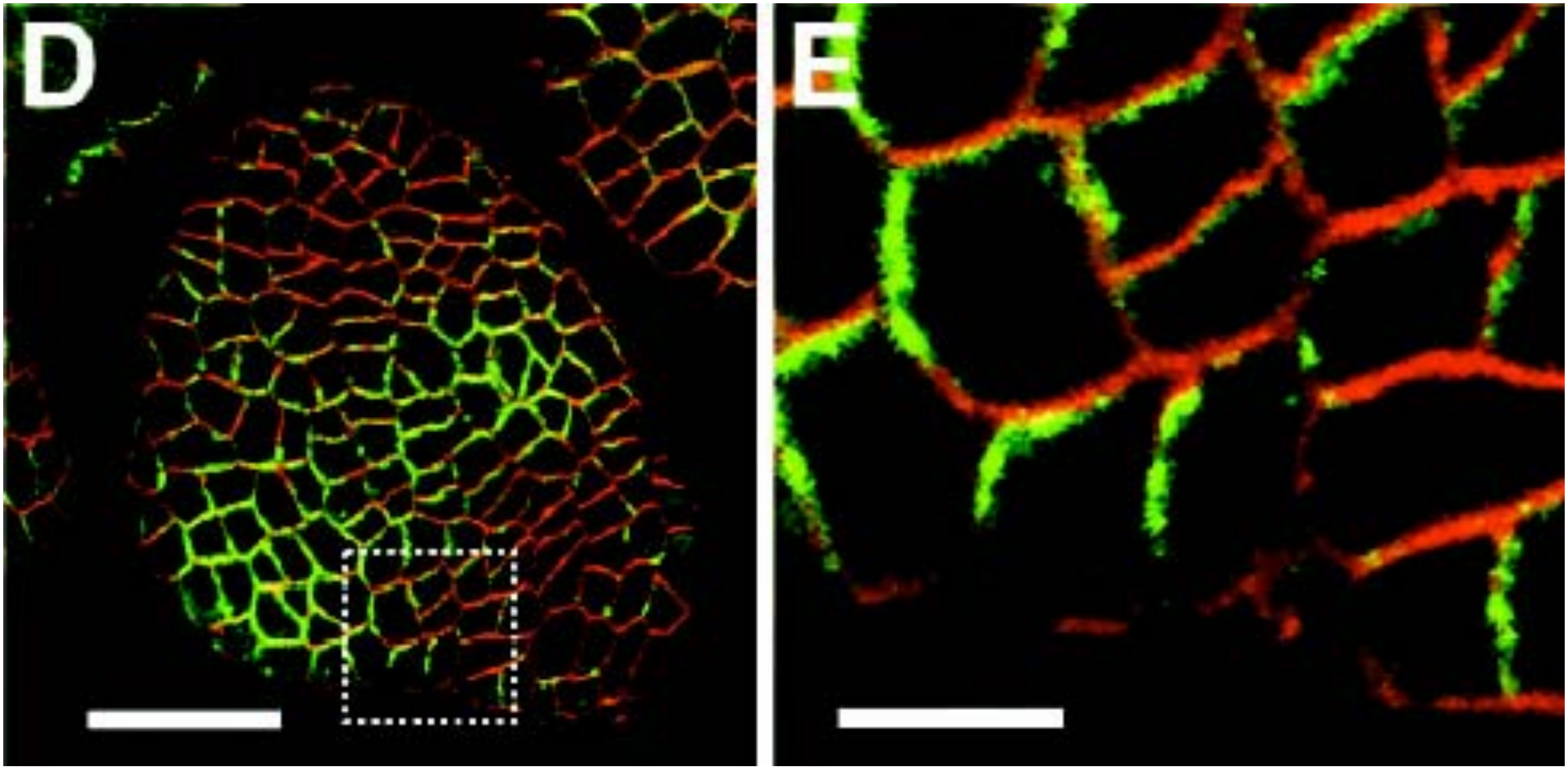
DG's at ≥ 3 scales:
- molecular;
- cellular;
- multicellular.

$$\left\{\texttt{auxin[i]} \xRightarrow{\texttt{PIN1[i,j]}} \texttt{auxin[j]},\ \emptyset \xRightarrow{\texttt{auxin[i]}} \texttt{PIN1[i]},\right.$$

$$\left.\texttt{PIN1[i]} \xRightarrow{\texttt{auxin[j]}} \texttt{PIN1[i, j]},\ \texttt{PIN1[i, j]} \to \emptyset,\ \texttt{PIN1[i, j]} \to \texttt{PIN1[i]}\right\}$$

[H. Jönnson, M. Heisler, B. Shapiro, E. Meyerowitz, E. Mjolsness - *Proc. Nat'l Acad. Sci.* 1/06]

Red: Plasma Membrane Dye
Green: PIN1-GFP



Heisler et al. Curr. Biol. 15:1899-1911.

Basic elements of the phyllotactic model

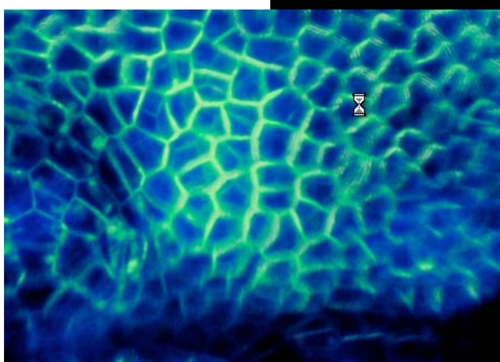
- Intracellular regulatory networks
- Polarized transport of auxin by PIN1
  - Positive feedback loop by hypothesized signal
    - ⇒Autoregulated transport
  - Auxin and its anion in boundary compartments
- Cell growth, mechanics, & division
- Dynamic topology of neighboring cells
  - *Weak spring* mechanical model

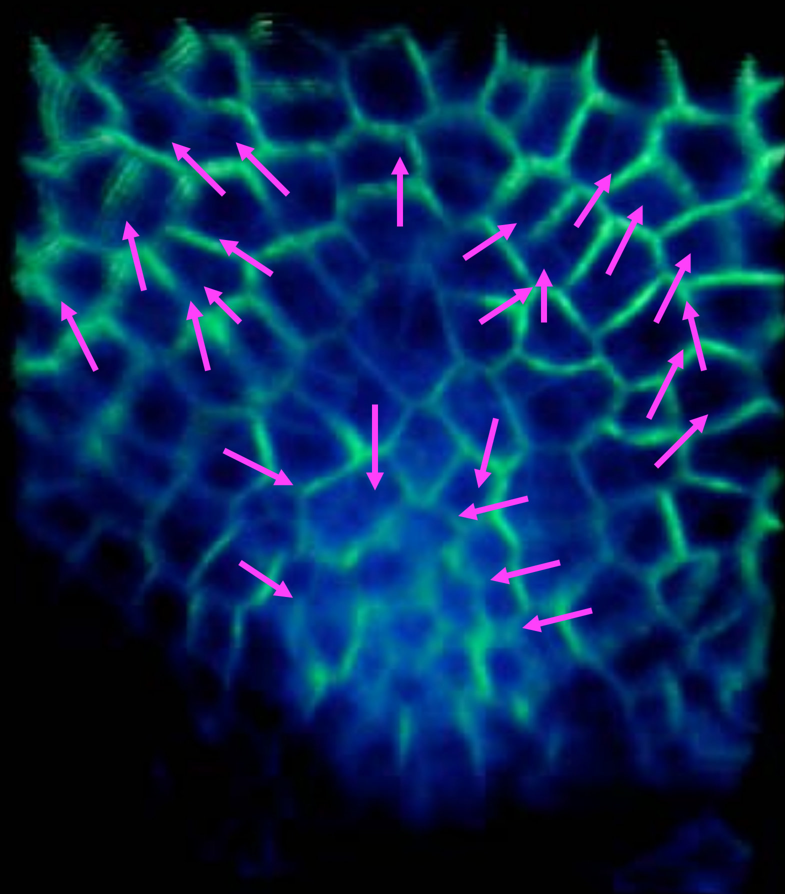
Auxin/PIN1 Details

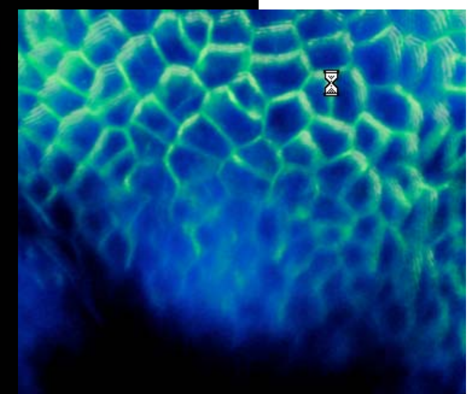
$$
\begin{aligned}
\frac{dA_i}{dt} &= c_A - d_A A_i + \frac{1}{V_i}\Bigg[p_{AH}\sum_{k\in\mathcal{N}_i} a_{ik}\left(f_{AH}^{wall}A_{ik} - f_{AH}^{cell}A_i\right) && \text{(S1)}\\
&+ \; p_{A^-}\sum_{k\in\mathcal{N}_i} a_{ik}P_{ik}\left(f_{A^-}^{wall}N_{influx}\frac{A_{ik}}{K_A+A_{ik}} - f_{A^-}^{cell}N_{efflux}\frac{A_i}{K_a+A_i}\right)\Bigg],\\
\frac{dA_{ij}}{dt} &= -d_A A_{ij} + \frac{1}{V_{ij}}\Big[a_{ij}\Big\{p_{AH}\left(f_{AH}^{cell}A_i - f_{AH}^{wall}A_{ij}\right) && \text{(S2)}\\
&+ \; p_{A^-}P_{ij}\left(f_{A^-}^{cell}N_{efflux}\frac{A_i}{K_a+A_i} - f_{A^-}^{wall}N_{influx}\frac{A_{ij}}{K_A+A_{ij}}\right)\Big\}\\
&+ \; D_A\left\{\frac{a_{ijij_l}}{d_{ijij_l}}\left(A_{ij_l}-A_{ij}\right) + \frac{a_{ijij_r}}{d_{ijij_r}}\left(A_{ij_r}-A_{ij}\right) + \frac{a_{ijji}}{d_{ijji}}\left(A_{ji}-A_{ij}\right)\right\}\Big],\\
\frac{dP_i}{dt} &= \frac{1}{V_i}\sum_k^{N_i} a_{ik}\left(k_2P_{ik} - P_i\frac{k_1A_k^n}{K^n+A_k^n}\right), && \text{(S3)}\\
\frac{dP_{ij}}{dt} &= P_i\frac{k_1A_j^n}{K^n+A_j^n} - k_2P_{ij}. && \text{(S4)}
\end{aligned}
$$

[H. Jönnson, M. Heisler, B. Shapiro, E. Meyerowitz, E. Mjolsness - *Proc. Nat'l Acad. Sci.* 1/06]

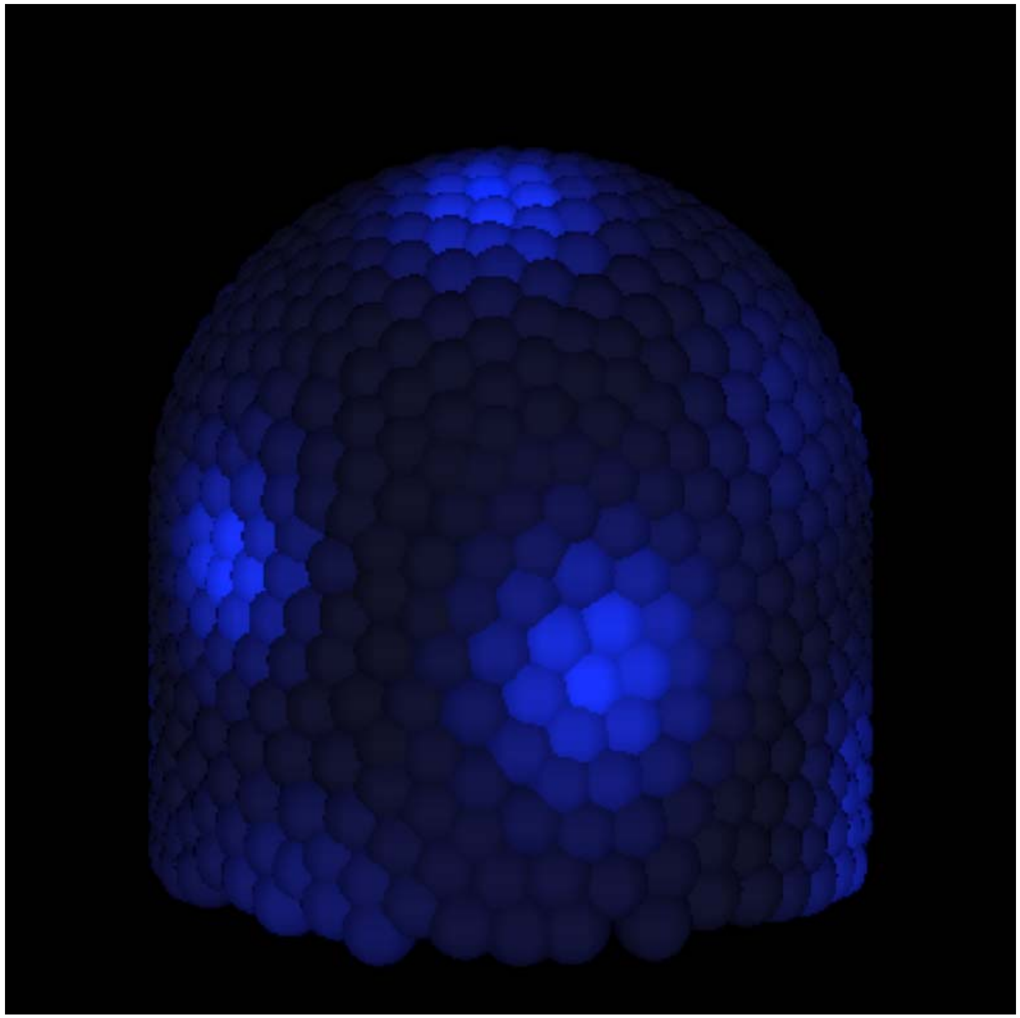
Polarity reversal is abrupt and has a sharp boundary



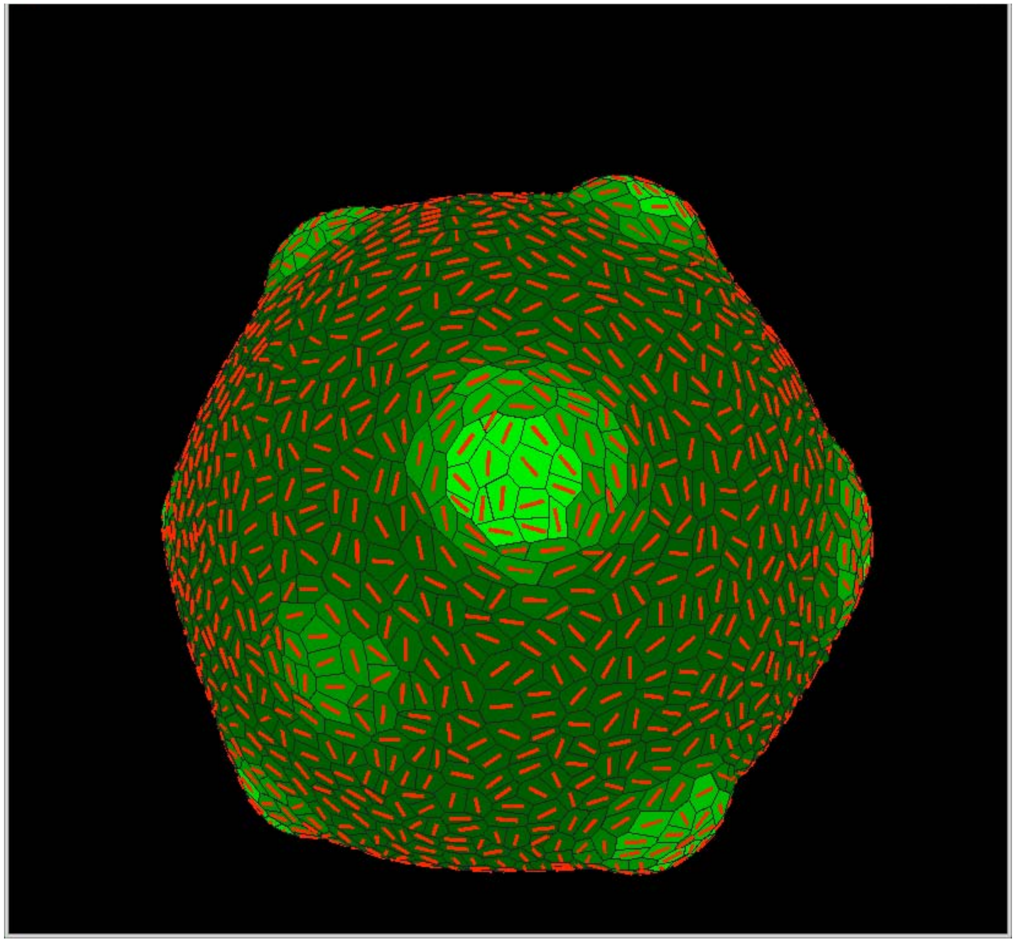




3D Visualization



Wall spring model



Henrik Jönsson 2008

Methods

- Hybrid systems
- Homotopy methods
- Finite element methods

Dynamic-PIN1 root (stele) model

- Sources
  - [Likhoshvai et al ICSB 2007]
  - [Likhoshvai et al. Russ. J. Dev. Biol. 2007] (pdf)
  - http://www.springerlink.com/content/51l86mj315438l67/?p=a03c85c87c8d4872aa17ce98938765d1&pi=4
- Methods
  - Two-mechanism model (~C. Kuhlemeir suggestion?)
  - Model reduction eliminates PIN

$$\frac{da_n}{dt} = \alpha + P_t a_{n-1} - P_t a_n - K_d a_n - K_0 a_n f(a_n),$$

$$\frac{da_i}{dt} = P_t(a_{i+1} + a_{i-1}) + K_0 a_{i+1} f(a_{i+1})$$

$$-2P_t a_i - K_d a_i - K_0 a_i f(a_i), \quad i = \overline{n-1, 2},$$

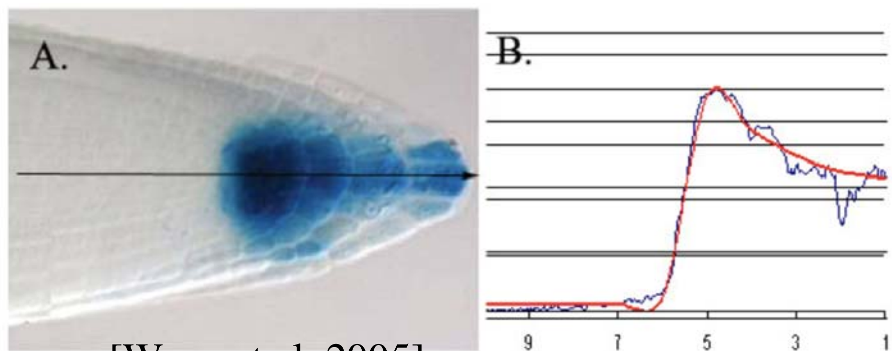
$$\frac{da_i}{dt} = -P_t a_1 - K_d a_1 + P_t a_2 + K_0 a_2 f(a_2),$$

$$f(a_i) = \left(\frac{\left(\frac{a_i}{q_{11}}\right)^{p_1}}{1 + \left(\frac{a_i}{q_{12}}\right)^{p_1}} \right) \times \left(\frac{1}{1 + \left(\frac{a_i}{q_2}\right)^{p_2}} \right),$$

  - Homotopy method finds steady states [Fadeev 1998]

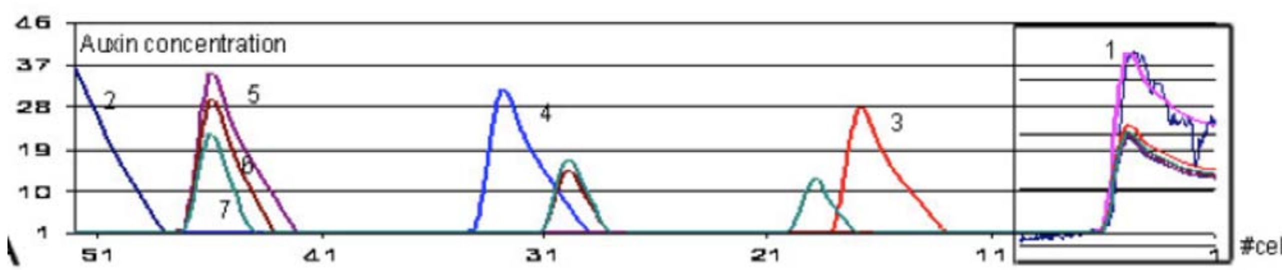
Root (stele) model results

- Auxin near the tip



[Wang et al. 2005]

- Possible lateral LH initiation steady states



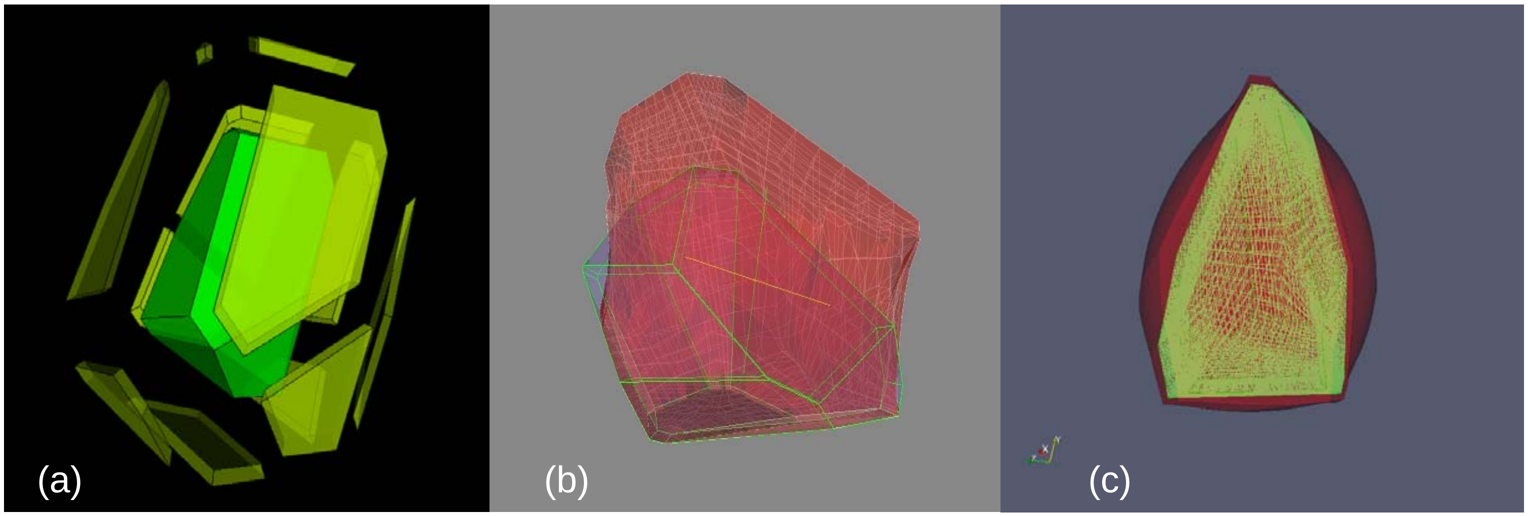
Software: STEP [Fadeev]

Methods

- Hybrid systems
- Homotopy methods
- Finite element methods

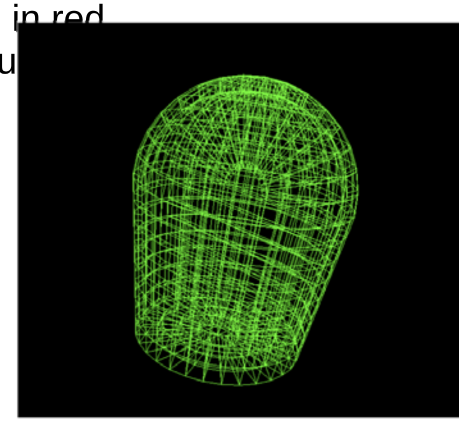
"Cell complex" framework:

Plant cell mechanical model



(a) 3D polyhedral model of plant cell. Expanded view shows separate walls (yellow) and cytoplasm (green). (b) FEM simulation of model cell deformation. Original cell was held at the bottom, stretched and twisted by 30^{o}. Resulting shape and mesh shown in red. Original cell given as the green outline. (c) The same cell expanding under u pressure. Result of simulation shown in red; original cell in green.

(d): Arabidipsis embryo FEM grid.



[Figures courtesy Pawel Krupinski, UCI/Lund,

Computable Plant project . ICSB 2007]

All quantities of interest (stresses, strains) are evaluated in discrete Gauss points, so they can be easily integrated or interpolated.

$$\int_{-1}^{1}\int_{-1}^{1}\int_{-1}^{1} g(\xi,\eta,\zeta)\, d\xi\, d\eta\, d\zeta = \sum_{l=1}^{n_{\text{int}}} g(\tilde{\xi},\tilde{\eta},\tilde{\zeta}) W_l$$

$\tilde{\xi},\tilde{\eta},\tilde{\zeta}$: Gauss points

W_l : Gauss weights

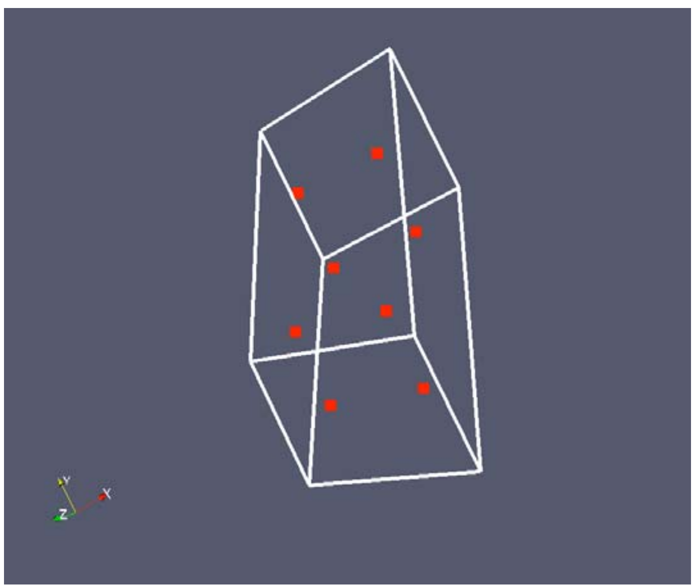
Gauss points are chosen to exactly integrate finite degree polynomials over the domain

Eight point Gaussian quadrature rule

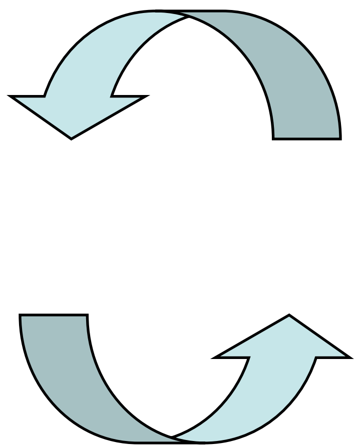
$$\tilde{\xi},\tilde{\eta},\tilde{\zeta} = \pm\frac{1}{\sqrt{3}}$$

$$W_l = 1$$

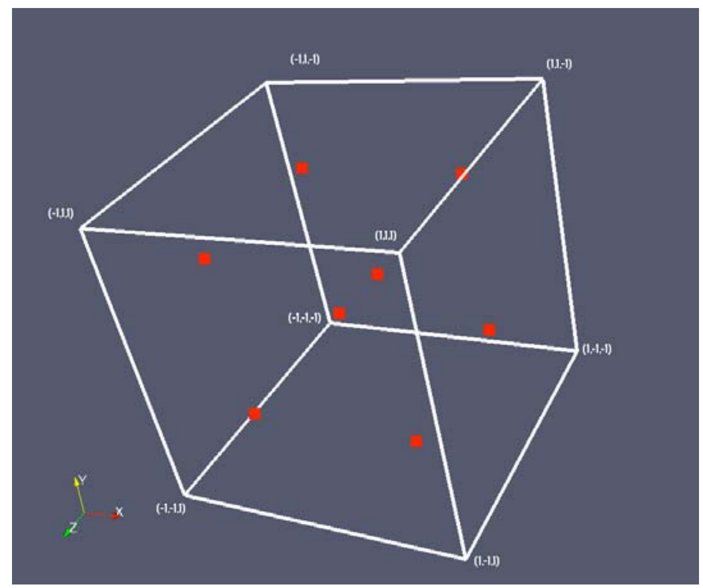
Integrates exactly 3-quadratic functions over the reference cube.



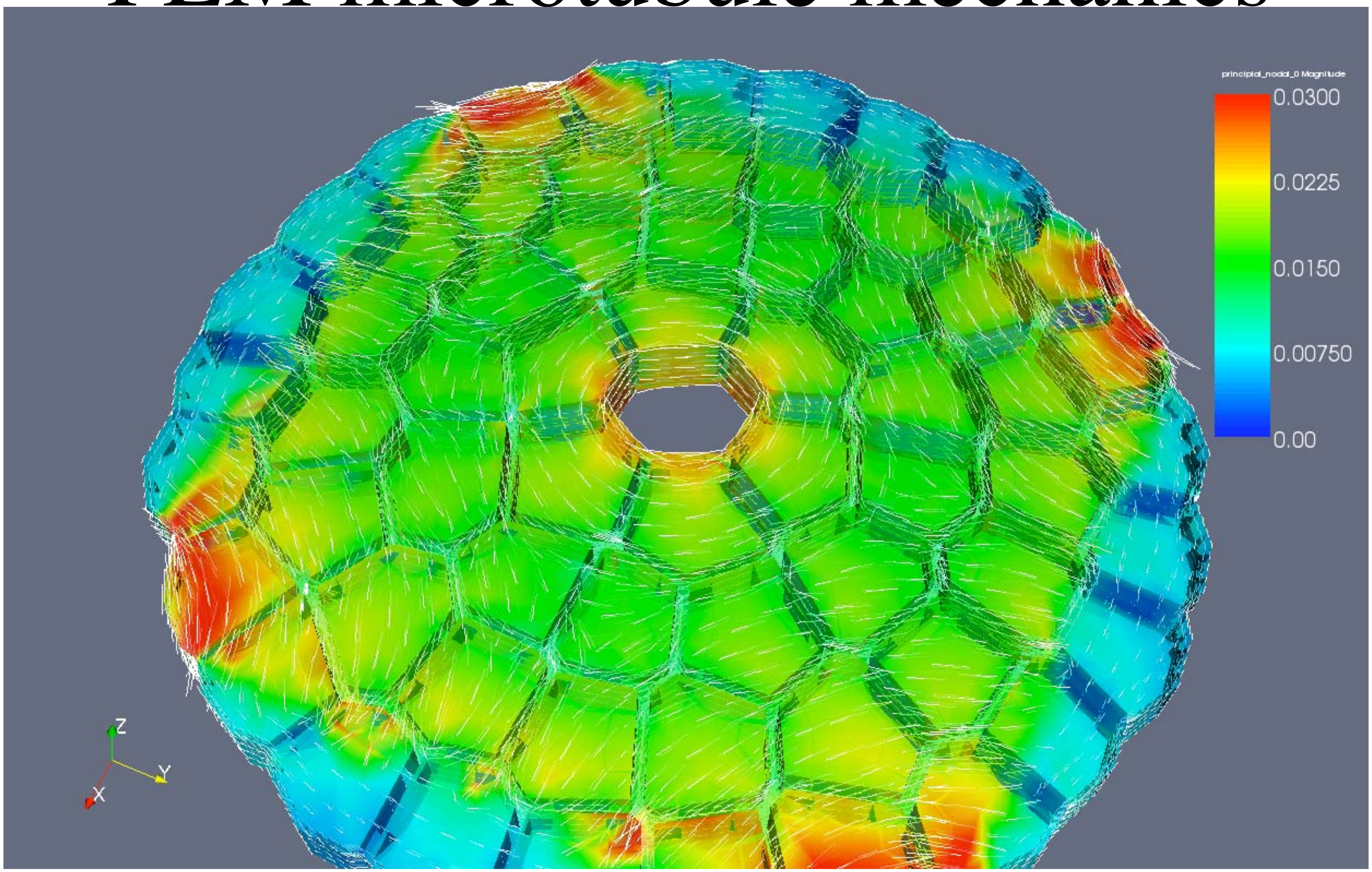
$\mathbf{x} = (x, y, z)$



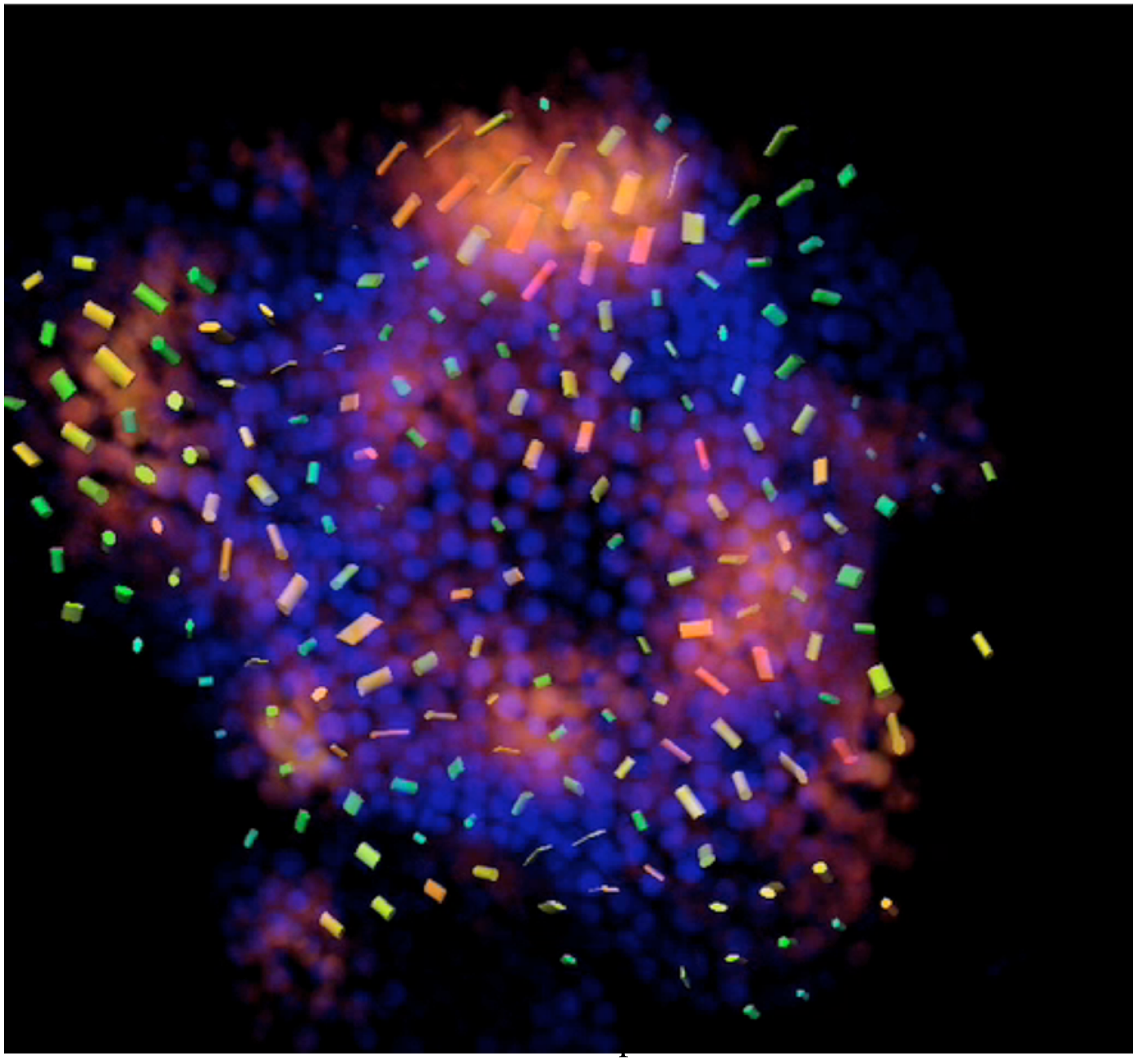
$\hat{\mathbf{\imath}} = (\xi,\eta,\varsigma)$



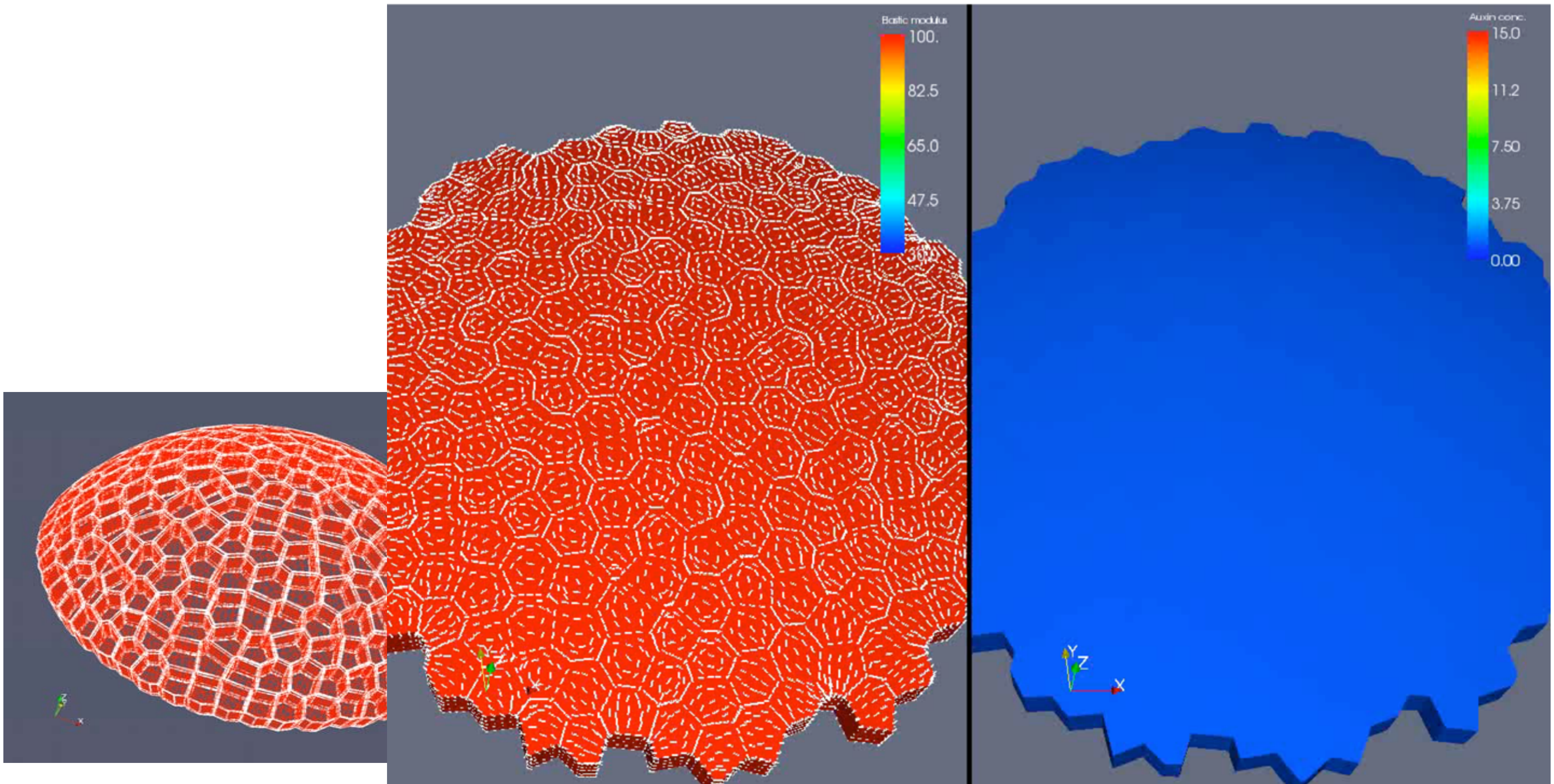
FEM microtubule mechanics



Principle components of Growth



Regulatory/FEM simulator



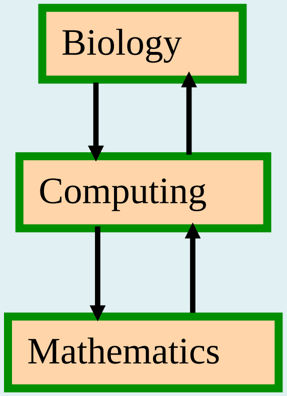
Pawel Krupinski, 2008

Methods

- Hybrid systems
- Homotopy methods
- Finite element methods
  - (cell division requred)

Outline: Math. Methods

- Statistical Mechanics
  - SM in metabolism, transcription
- Stochastic Dynamics
  - Operator algebra
- Classical Spatial Dynamics
  - Hybrid systems; elastic dynamics
- Computational Dynamics
  - Semantics
  - Computational Morphodynamics



Methods

- Semantics:
  - Dynamical Grammars process composition language
- Multiscale methods
- Graph Transformations
- Parameter estimation
- Computational Morphodynamics

SPG Modeling Language: Semantics

Semantic map $\Psi: \Gamma \rightarrow H$
from Grammar to Stochastic Process

- Commutative diagrams for composition operations

$$
\begin{tikzcd}
\Gamma \arrow[rr, "\cup"'] \arrow[d, "\Psi"'] & & \Gamma' \arrow[d, "\Psi"] \\
H,\ dp/dt \arrow[rr, "\Sigma"] & & H',\ dp'/dt
\end{tikzcd}
$$

- Transla

define the rule's generator

$$\tilde{O}_r = \rho_r \sum_{\{x'_i, x_j\}} \prod_{i \in \mathrm{rhs}(r)} \hat{a}(\tau_i, x_i) \prod_{j \in \mathrm{lhs}(r)} a(\tau_j, x_j) \Pr(\{x_i\} \mid \{x_j\})$$

$$O_r = \tilde{O}_r - \mathrm{diag}\left(\mathbf{1}^T \cdot \tilde{O}_r\right)$$

Operator Algebra Specifies Stochastic Process Semantics

- Grammar rule: $\boxed{\{\tau_i(x_i)\} \to \{\tau'_j(y_j)\} \text{ with } \rho_r((x_i), (y_j))}$
  - E.g. reaction net:

$$\{m_i^{(r)} A_i\} \xrightarrow{k^{(r)}} \{n_i^{(r)} A_i\} \qquad H = \sum_{r=1}^{R} k^{(r)} \left[\left(\prod_{i=1}^{I} (\hat{a}_i)^{n_i^{(r)}} \right) \left(\prod_{i=1}^{I} (a_i)^{m_i^{(r)}} \right) - \prod_{i=1}^{I} (N_i)_{m_i^{(r)}} \right]$$

- Semantics (Pr(y|x) given e.g. by Dependency Diagram)

define the rule's generator

$$\tilde{O}_r = \rho_r \sum_{\{x'_i, x_j\}} \prod_{i \in \mathrm{rhs}(r)} \hat{a}(\tau_i, x_i) \prod_{j \in \mathrm{lhs}(r)} a(\tau_j, x_j) \Pr(\{x_i\} \mid \{x_j\})$$

$$O_r = \tilde{O}_r - \mathrm{diag}\left(\mathbf{1}^T \cdot \tilde{O}_r\right)$$

$$H = \sum_r O_r . \qquad \frac{d}{dt} \Pr(t \mid 0) = H \Pr(t \mid 0). \qquad \Pr(t \mid 0) = e^{tH} \Pr(0)$$

  - Variable-binding by summation/integration

[Annals of Math. and A. I., 47(3-4), January 2007]

Operator Algebra Composition Operations: +, *, exp, Π, *d/dx*, *δ/δf(x)*

Operator algebra	Informal meaning	Γ Syntax
• $H_1 + H_2$	• *independent, parallel* occurrence	• parallel rules
• $H_1 * H_2$ (noncommutative)	• *instantaneous, serial* co-occurrence	• Multiple terms on LHS, RHS
• exp $t\,H$ (for large t) (can be recursive) • Projection, $\Pi^2 = \Pi$	• time evolution (possibly fast) • subroutine call (information hiding)	• Invocation or **via** keyword • **via** keyword
• $(d/dx)^n$ – functional derivatives – $(\delta/\delta f(x))^n$	• Spatial limits: – ODE's – Diffusion/drift SDE's – PDE's, SPDE's	• **solve** keyword

DG reaction-rule **keywords**

Importance	Keyword	introduces rate modifier expression ...	semantics
Essential			
	with	probability rate function	discrete transition operator, or factor thereof
	solving	differential equation	differential operator, or sumand thereof
Increased expressiveness			*limits* of the essential ones
	subject to	constraint	delta function factor in discrete transition operator
	via	sub-grammar invocation	exponential factor $\exp(T\ W)$ in discrete transition operator
	solving	functional differential equation	functional differential operator
Convenience options			
	substituting	macro grammar expansion	semantics after expansion
	under	Boltzman energy function	related to **with**
	where	constraint	same as **subject to**

Composition of Processes

- Parallelism:
  - Union of reactions → sum of operators
- Submodels:
  - subgrammar (***via***), macro (***substituting***)
- Inheritance

Expressiveness progression

- Reaction-like processes
  - Mass action
  - Algebraic rate laws
  - Stochastic events (operator algebra foundation; graph notations)
  - Indexed reaction schema (eg. molecular complexes, fixed spatial models)
- Generalized reactions
  - Parameterized reactants; Stochastic Parameterized Grammars
  - Variable-structure systems (VSS)
  - Graph grammars (GG), eg. via object identifier indices
  - *Cell (CW) complexes*
- Dynamical Grammars
  - Add in ODEs, *PDEs, SPDE's*
  - *Lively geometries & cell complexes (perhaps stochastic)*

Methods

- Semantics:
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Multigrid in off-grid OE example

$$\{c = INP::Cell(x, r),\ g = Signal\_Field\ (\phi)\} \to \{c, g\}, \qquad \textbf{solving}\ \left\{\frac{\partial\phi}{\partial t} = k_I(x, r)\right\}$$

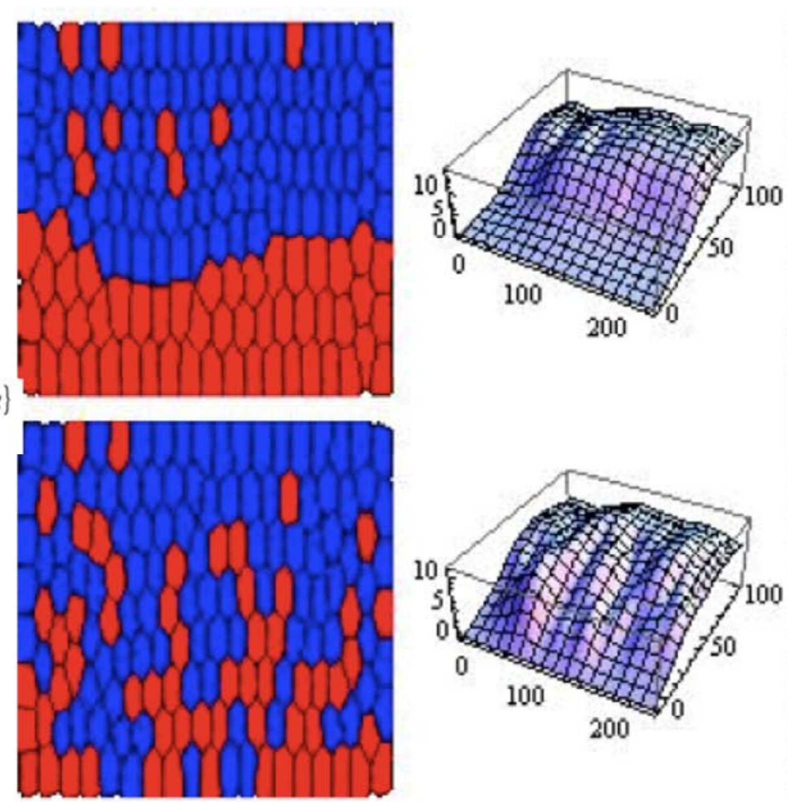
$$\{c = ORN::Cell(x, r),\ g = Signal\_Field\ (\phi)\} \to \{c, g\}, \qquad \textbf{solving}\ \left\{\frac{\partial\phi}{\partial t} = k_O(x, r)\right\}$$

$$Signal\_Field\ (\phi) \to Signal\_Field\ (\phi)$$

$$\textbf{solving}\ \left\{\frac{\partial\phi}{\partial t} = D\,\frac{\partial^2\phi}{\partial x^2} - d\,\phi\right\}$$

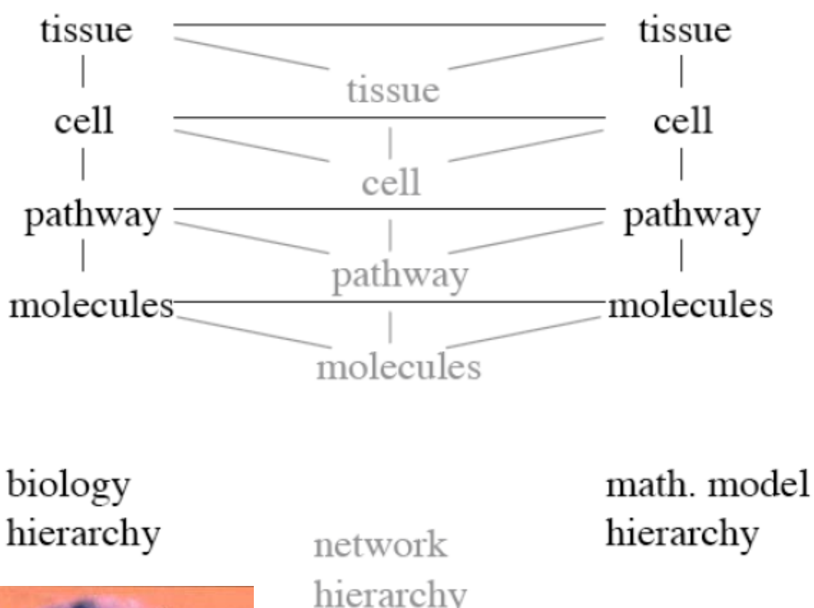
$$\{INP::Cell(x, r),\ g = Signal\_Field\ (\phi)\} \to \{ORN::Cell(x_1, r/2^{1/d}),\ ORN::Cell(x_2, r/2^{1/d}),\ g\}$$

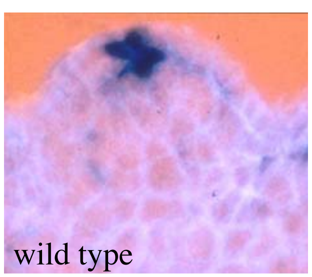
$$\textbf{with}\ \rho_{2,2}(\phi(x))\,P(x_1, x_2 \mid x)/T$$



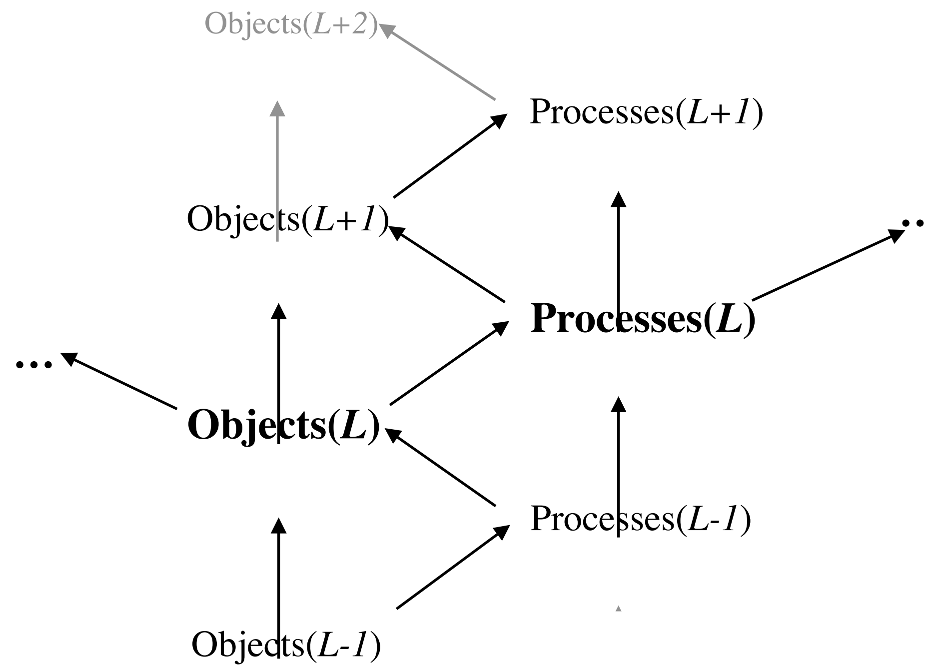
Biological scale hierarchies

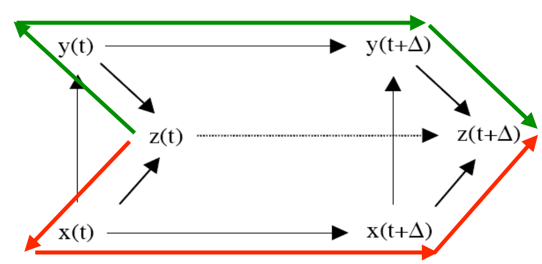
Biology, networks, & models:





Noun and verb hierarchies:





Graph → Dynamics frameworks

- Sparse matrix → GRN model
- Labelled bipartite reaction graph → ODE model (eg. Sigmoid)
- Multiset rewrite rule graph → stochastic models

- … all permit graph reduction → model reduction

Methods

- Semantics:
  - Dynamical Grammars process composition language
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- Parameter estimation
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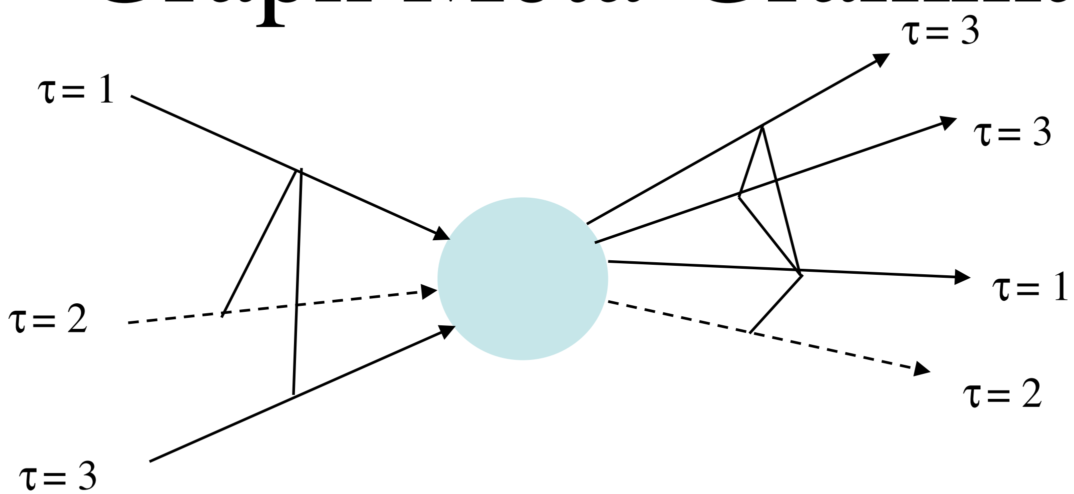
Graph Meta-Grammar



$$\Gamma = \{ \left\{ A_i = \mathrm{term}\left(\boldsymbol{\tau}_i, \mathbf{x}_i, \left[A_{\sigma(i,\alpha)} \middle| \alpha \in \mathrm{A} \right]\right) \middle| i \in I \right\}$$

$$\rightarrow \left\{ A'_j = \mathrm{term}\left(\boldsymbol{\tau}'_j, \mathbf{x}'_j, \left[A'_{\sigma(j,\beta)} \middle| \beta \in \mathrm{B} \right]\right) \middle| j \in I \right\}$$

$$\text{with} \quad \Gamma^r_{\tau;\tau'} \in [0,1]$$

$$\}$$

Graph Grammar Example

grammar (discrete-time) *graph-recursion* (start $\rightarrow$ {node($\mathbf{i}$), G-connection($a, \mathbf{i}, \mathbf{j}$) }) {

start $\rightarrow$ node((0)), $G - connection(1, (0), (0))$

N=node($\mathbf{i}$) $\rightarrow$ N=node($\mathbf{i}$), { node(($\mathbf{i}, i_n$))$|A_{(\mathbf{i},i_n)} = 1_n^i < i_{max}$ }

under $E = \mu \sum_{(\mathbf{i},i_n)} A_{(\mathbf{i},i_n)}$

G-connection($a, \mathbf{i}, \mathbf{j}$), N=node(($\mathbf{i}, i_n$)), M=node(($\mathbf{j}, j_n$))

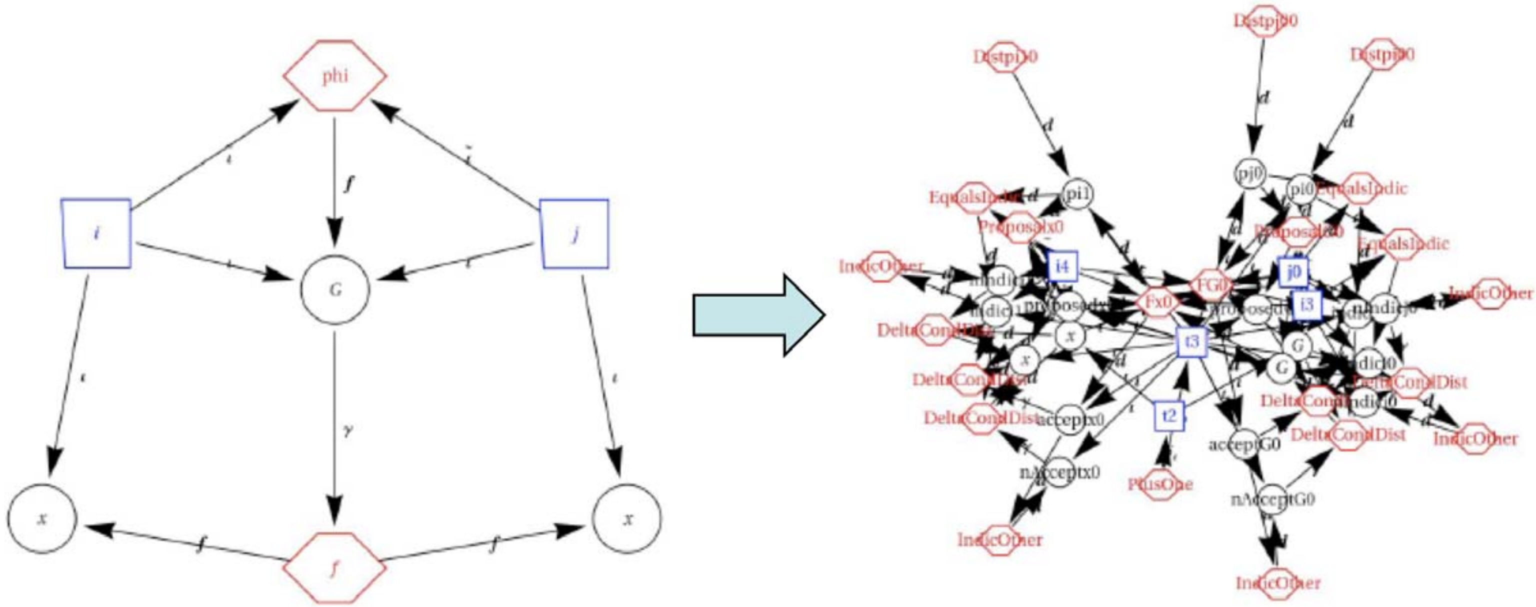
$\rightarrow$ { G-connection(b, ($\mathbf{i}, i_n$), ($\mathbf{j}, j_n$))$|G^{ab}_{i_n j_n} = 1$ }, N, M

}

$$G^{a_0}_{(i_1 \ldots i_L)(j_1 \ldots j_L)} = \sum_{\{a_l\}} \prod_{l=1}^{L} (G^{(a_{l-1} a_l)}_{(i_l j_l)})^{A_{(i_1 \ldots i_L)} A_{(j_1 \ldots j_L)}}$$

Eg. Graph Prior,

graphically transformed to MCMC algorithm



$$E_{\mathrm{GP}}(G, x) = C_1 \sum_{ij} G_{ij}(\|\mathbf{x}_i - \mathbf{x}_j\| - d)^2 + \psi_{\mathrm{CMP}}(\textstyle\sum_{ij} G_{ij} | \lambda, v)$$

Graph Grammars in DG's:

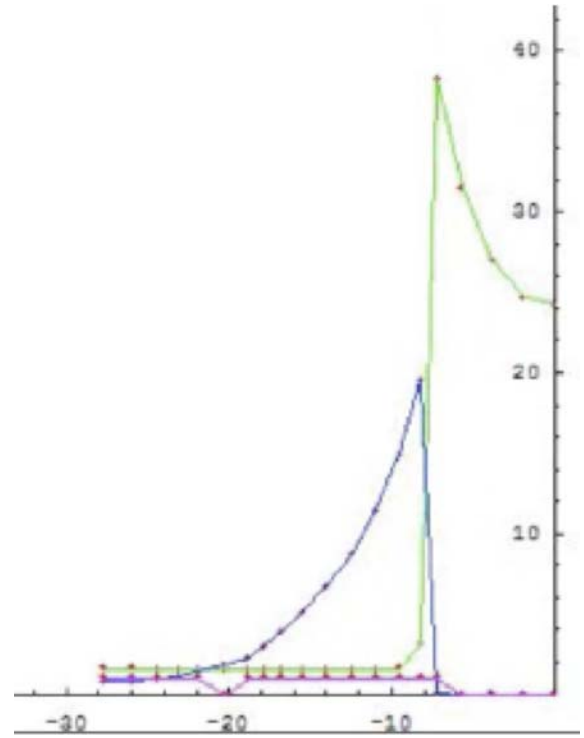
Root growth model in Plenum

```
(*change cell mode from growth to wait,when over a radius threshold *)
cell[cellID, 1, loc, rad, auxin, y, cellIDPrev, cellIDNext] →
 cell[cellID, 2, loc, rad, auxin, y, cellIDPrev, cellIDNext],
with[gGrowthModelMult * stopGrowthConst * grammarSigmoid[
   rad - gLimitCellRad, gDivideTemp]],

(*divide a cell when its in wait mode*)
cell[cellID, 2, loc, rad, auxin, y, cellIDPrev, cellIDNext] → {
  cell[cellIDPrev, cModeP, locP, radP, auxinP, yP, cellIDPP, cellID] →
   cell[cellIDPrev, cModeP, locP, radP, auxinP, yP, cellIDPP, grammarCreateObjectID[1]],
  cell[cellIDNext, cModeN, locN, radN, auxinN, yN, cellID, cellIDNN] →
   cell[cellIDNext, cModeN, locN, radN, auxinN, yN, grammarCreateObjectID[2], cellIDNN],

  cell[grammarCreateObjectID[1], 1, loc - rad + 2 rad * cellpart + rad * (1 - cellpart),
   rad * (1 - cellpart), auxin, y, cellIDPrev, grammarCreateObjectID[2]],
  cell[grammarCreateObjectID[2], 1, loc - rad + rad * cellpart, rad * cellpart,
   auxin, y, grammarCreateObjectID[1], cellIDNext]},
with[gGrowthModelMult * yEffectOnDivisionFunc[y] * grammarPDF[
   UniformDistribution[0.5 - gRangeParam, 0.5 + gRangeParam], cellpart]],


(* auxin active transport from previous cell*)
{c0 == cell[cellID0, cMode0, loc0, rad0, auxin0, y0, cellIDP0, cellID1] ,
  c1 == cell[cellID1, cMode1, loc1, rad1, auxin1, y1, cellID0, cellIDNext]} → {c0, c1},
solving[auxin1′ == k0 auxin0 func[auxin0], auxin0′ == -k0 * auxin0 func[auxin0]],
```



Vika Miranova (ICG) and Guy Yosiphon (UCI)

Graph Grammars → DG's

- In general:

$$\left\{L_{\lambda(i)} := \tau_i\left(x_{a(i)}; \left(L_{N(i,\sigma)} \,\middle|\, \sigma \in 1..\sigma_{a(i)}^{\max}\right)\right) \,\middle|\, i \in \mathcal{I}\right\}$$
$$\to \{L_{\lambda(i)} \mid i \in \mathcal{I}_1 \subseteq \mathcal{I}\} \cup \left\{L_{\lambda'(j)} := \tau_j\left(x'_{a'(j)}; \left(L_{N'(j,\sigma)} \,\middle|\, \sigma \in 1..\sigma_{a'(j)}^{\max}\right)\right) \,\middle|\, j \in \mathcal{J}\right\}$$
$$\textbf{with } \rho_r\left(\left\{x'_{a'(j)}\right\} \,\middle|\, \{x_{a(i)}\}\right)$$

- … translates to

$$\{\tau_{a(i)}(L_{\lambda(i)}, x_{a(i)}, (L_{N(i,\sigma)} \mid \sigma \in 1..\sigma_i^{\mathrm{cur}})) \mid i \in \mathcal{I}\}, \ \mathrm{OIDGen}(\mathrm{NextOID})$$
$$\to \{\tau_{a(i)}(L_{\lambda(i)}, x_{a(i)}, (L_{N(i,\sigma)} \mid \sigma \in 1..\sigma_i^{\mathrm{cur}})) \mid i \in \mathcal{I}_1\} \cup$$
$$\left\{\tau_{a'(j)}\left(L_{\lambda'(j)}, x'_{a'(j)}, \left(L_{N'(j,\sigma)} \,\middle|\, \sigma \in 1..\sigma_j^{\mathrm{cur}}\right)\right) \,\middle|\, j \in \mathcal{J}_1 \wedge (i \in \mathcal{I}_2) \wedge (\lambda(i) = \lambda'(j))\right\} \cup$$
$$\left\{\tau_{a'(j)}\left(L_{\lambda'(j)}, x'_{a'(j)}, \left(L_{N'(j,\sigma)} \,\middle|\, \sigma \in 1..\sigma_j^{\mathrm{cur}}\right)\right) \,\middle|\, j \in \mathcal{J}_2\right\} \cup \{\mathrm{Null}(L_{\lambda(i)}) \mid i \in \mathcal{I}_3\}$$
$$\bigcup \{\mathrm{OIDGen}(\mathrm{NextOID} + |\,\mathcal{J}\,|)\}$$
$$\textbf{with } \rho_r\left(\left\{x'_{a'(j)}\right\} \,\middle|\, \{x_{a(i)}\}\right) \prod_{j \in \mathcal{J}_2} \delta_K(L_{\lambda'(j)}, \ \mathrm{NextOID} + j - 1)$$

[Annals of Math. and A. I., 47(3-4), January 2007]

Algebra(Graph Grammars) → Algebra(DG's)

- Eg. insert amarked item into and remove it from a list

$$\langle A(u),\ \ A(u)\rangle,\ A(m) \to \langle A(u),\ \ A(m),\ A(u)\rangle$$

$$\langle A(u),\ \ A(m),\ \ A(u)\rangle \to \langle A(u),\ \ A(u)\rangle,\ \ A(m)$$

- DG

$$\hat{O}_{\text{remove}}\ \hat{O}_{\text{insert}} = \left(\sum_{i\,j\,l\,k} \hat{a}_m\ \hat{a}_{i\,j\,u}\ \hat{a}_{j\,k\,u}\ a_{i\,j\,u}\ a_{j\,k\,m}\ a_{k\,l\,u}\right)\left(\sum_{i\,j\,l\,k} \hat{a}_{i\,l\,u}\ \hat{a}_{l\,j\,m}\ \hat{a}_{j\,k\,u}\ \hat{o}_{l+1}\ \ a_{i\,j\,u}\ a_{j\,k\,u}\ a_m\ o_l\right)$$

$$= \left(\sum_{i\,j\,l\,k}\ \sum_{i'\,j'\,k'\,l'} \hat{a}_m\ \hat{a}_{i'\,l'\,u}\ \hat{a}_{l'\,k'\,u}\ a_{i'\,l'\,u}\ a_{l'\,j'\,m}\ a_{j'\,k'\,u}\ \hat{a}_{i\,l\,u}\ \hat{a}_{l\,j\,m}\ \hat{a}_{j\,k\,u}\ \hat{o}_{l+1}\ \ a_{i\,j\,u}\ a_{j\,k\,u}\ a_m\ o_l\right)$$

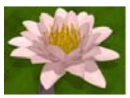
- GG algebra (result of a calculation):

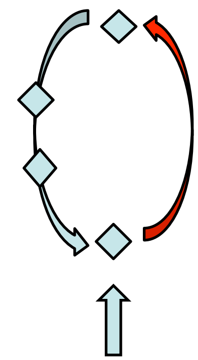
$$\hat{O}_{\text{remove}}\ \hat{O}_{\text{insert}} = \sum_{i\,j\,k\,l\ \text{all} \neq} \hat{a}_{i\,l\,u}\ \hat{a}_{l\,k\,u}\ \hat{o}_{l+1}\ \ a_{i\,j\,u}\ a_{j\,k\,u}\ o_l$$

$$= \sum_{i\,j\,k\,l\ \text{all} \neq} \hat{O}(\{\langle A(i,\ j,\ u),\ \ A(j,\ k,\ u)\rangle,\ \text{OIDGen}(l)\} \to \{\langle A(i,\ l,\ u),\ \ A(l,\ k,\ u)\rangle,\ \text{OIDGen}(l+1)\})$$

$$\simeq I$$

CMD Modeling Frameworks

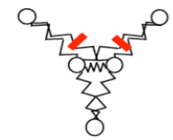
- Generalized reactions
  - SPG's and DG's (local topology = multiset)
  -  L-systems (local topology = string)
  - P-systems (local topology = tree+multiset)
  - Graph grammars (local topology = graph)
  - Cell complexes (local topology = cell complex)

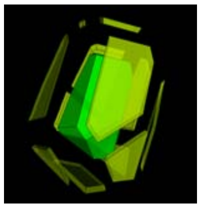


- Spatial continuua
  - PDE's
  - Cellular Potts models
  - Spatial stochastic models
  - Lively manifolds & CW cell complexes

Styles of Developmental Model

- Turing: reaction/diffusion
- PDE's: can add growth, cell polarity, …
- Cellular/compartmental
  - Weak spring, FEM, lively cell complex, …
- Image-driven
- Spatially stochastic
- Unified (any or all of the above)





Methods

- Semantics:
  - Dynamical Grammars process composition language
- Multiscale methods
- Graph Transformationa
- Parameter estimation
- Computational Morphodynamics

Bayesian outline of scientific process **elements** and *techniques*

Posterior = likelihood * prior/ evidence:

$$P(M \mid D) = \frac{P(D \mid M, D_{old}) \, P(M \mid D_{old})}{P(D \mid D_{old})}$$

- D= data = $D_{old} + \Delta D$: **observation, experiment**
- M = model or theory
- $P(M \mid D_{old})$: *deep hierarchical prior* on models
  ~ **judgment** of a scientific *agent*
- $P(D \mid M, D_{old}) \, P(M \mid D_{old})$: *optimization, simulation*
  => **formulate hypothesis** M^*
- $P(D \mid M, D_{old})$: *simulation, analysis, proof* => **draw consequences**

Bayesian outline, continued

$$P(M \mid D) = \frac{P(D \mid M, D_{old}) \, P(M \mid D_{old})}{P(D \mid D_{old})}$$

- Evidence term, $P(D \mid D_{old}) = \sum_{M'} P(D \mid M', D_{old}) \, P(M' \mid D_{old})$:

  Consider **alternative hypotheses**
  - *Imaginative exploration* of mathematical frameworks
  - *Model reduction* and *model integration*: find noncompeting models
  - Uniqueness: ideally $\sum_{M'} P(D \mid M', D_{old}) \, P(M' \mid D_{old}) \approx P(D \mid M^{*}, D_{old}) \, P(M^{*} \mid D_{old})$

    => find future **critical experiments**
  - Grand challenge: *sample the evidence term* Σ_M [e.g. Girolami; Werhli]
- P(M | D) : **revision** of agent judgment

  => possible **paradigm shift** in deep structure likelihoods

Dependency Diagrams

for probability distributions

$$\Pr(\mathbf{x}) = \frac{1}{Z} \prod_{\kappa \in \mathcal{K}_1} \phi_\kappa(\{x_i | F_{i\kappa} = 1\})^{\left(\prod_{k|\gamma(\kappa,k)=1} \mathbf{1}(x_k > 0)\right)}$$

$$\times \prod_{\kappa \in \mathcal{K}_2} \phi_\kappa(\{x_i | D_{i\kappa} = 1\} | \{x_j | D_{\kappa j} = 1\})^{\left(\prod_{k|\gamma(\kappa,k)=1} \mathbf{1}(x_k > 0)\right)}$$

Table 1: One possible rendering of dependency diagrams

Algebraic expressions	Full name	Rendering
F	factor link	f link
D	conditional dependency	d link
ι	index link	ι link
$\hat{\iota}$	argument index link	$\hat{\iota}$ link
γ	gating link	γ link
δ_ι	index constraint link	δ link
x	random variable	circle node, x
θ = various symbols	model parameter	double circle node, θ
ϕ	factor	hexagon node, ϕ
a	index	square node, a

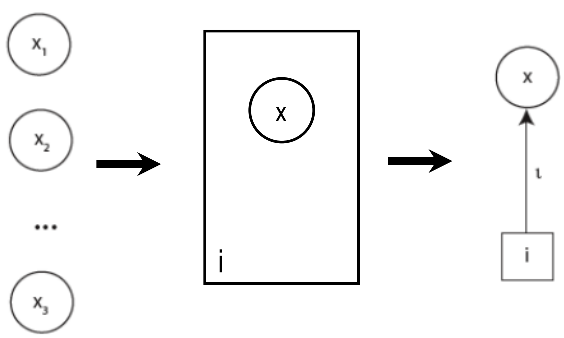
Index Nodes and Links, ι

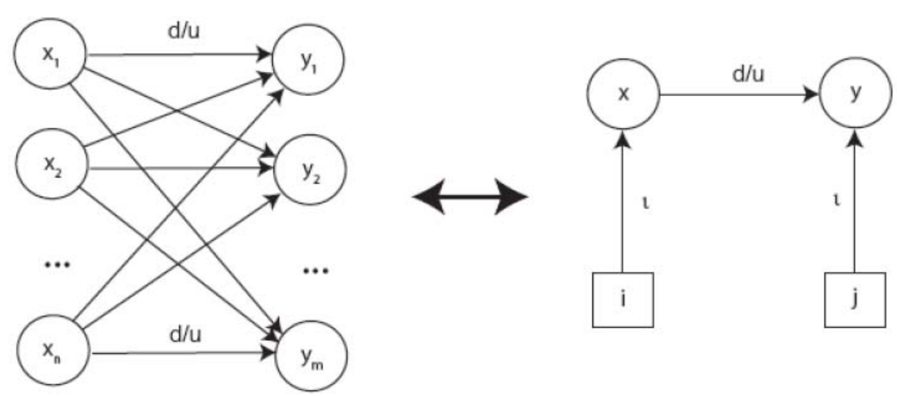
- Rationale
  - param sharing
  - structured models
  - compact diagrams
- Precedent: Plates
  - [Buntine JAIR 1994]
  - Disaggregate plates into index noc (platelets) and general-purpose "groups"
- Semantics, 1-level (w. *u*, *a*, *d*)

$$\Pr(\{x\}) = \boxed{\prod_{\{a_\alpha \in \mathcal{I}_\alpha\}}} \prod_{\{i \in \mathcal{I}\}} \phi_{i,(a_\alpha | \alpha \mapsto_\iota i)}\left(x_{i,(a_\alpha | \alpha \mapsto_\iota i)} \,\middle|\, \left\{x_{j,(a_\beta | \beta \mapsto_\iota j)} \,\middle|\, j \mapsto_D i\right\}\right)$$

- Semantics, multi-level
  - for complex multiscale architectures

$$\Pr(\{x\}) = \boxed{\prod_{\{a_1 \in \mathcal{I}_{1,1}\}} \prod_{\{a_{\alpha=2, j_\alpha \in J_\alpha} \in \mathcal{I}_{1,2}\}} \cdots \prod_{\{a_{\alpha, j_\alpha \in J_\alpha} \in \mathcal{I}_{1,\alpha}\}} \cdots \prod_{\{a_{A, j_A \in J_A} \in \mathcal{I}_{1,A}\}}} \prod_{\{i \in \mathcal{I}_0\}} \phi_{i,(a_{\alpha, j_\alpha \in J_\alpha} | \alpha \mapsto_\iota i)}\left(x_{i,(a_{\alpha, j_\alpha \in J_\alpha} | \alpha \mapsto_\iota i)} \,\middle|\, \left\{x_{j,(a_{\beta, j_\beta \in J_\beta} | \beta \mapsto_\iota j)} \,\middle|\, j \mapsto_D i\right\}\right)$$





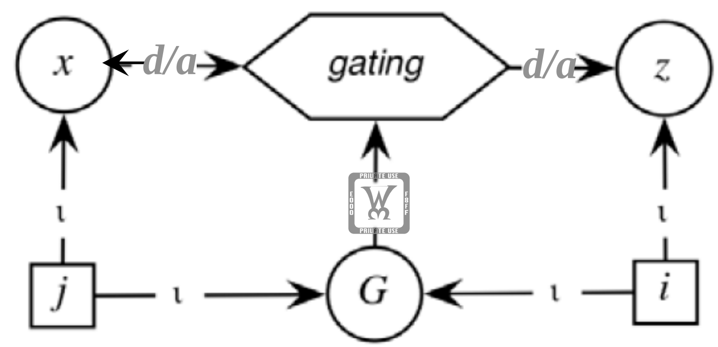
Gating Links, γ

- Rationale
  - Allows variable structure = modulated relationship presence.
  - Combined with sparseness constraint on gating vbls, gives basic new cost params (#*active* nodes/links)
- Precedent:
  - Mixture cluster models, MRF line processes, graph matching nets, Frameville, Mixture of Experts, circuit schematics, …

- Semantics: selective omission
  - modulates d, u, or a links (w or w/o)

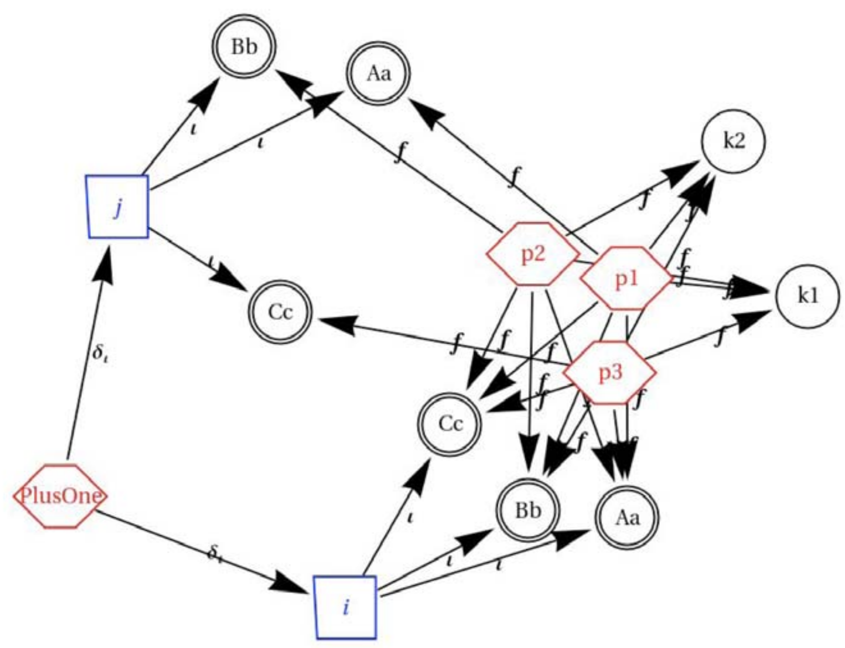
$$\Pr(\{x\}) = \frac{1}{Z} \prod_{\{a_1 \in \mathcal{I}_{1,1}\}} \prod_{\{a_{\alpha=2, j_\alpha \in J_\alpha} \in \mathcal{I}_{1,2}\}} \cdots \prod_{\{a_{\alpha, j_\alpha \in J_\alpha} \in \mathcal{I}_{1,\alpha}\}} \cdots \prod_{\{a_{A, j_A \in J_A} \in \mathcal{I}_{1,A}\}} \prod_{c \in C} \left[\phi_c\left(\left\{ x_{i,(a_{\alpha, j_\alpha \in J_\alpha} | \alpha \mapsto_\iota i)} \,\middle|\, c \mapsto_A i \right\}\right) \boxed{\prod_{j \,|\, j \mapsto_\gamma c} \Theta\left(x_{j,(a_\beta | \beta \mapsto_\iota j)}\right)} \right]$$

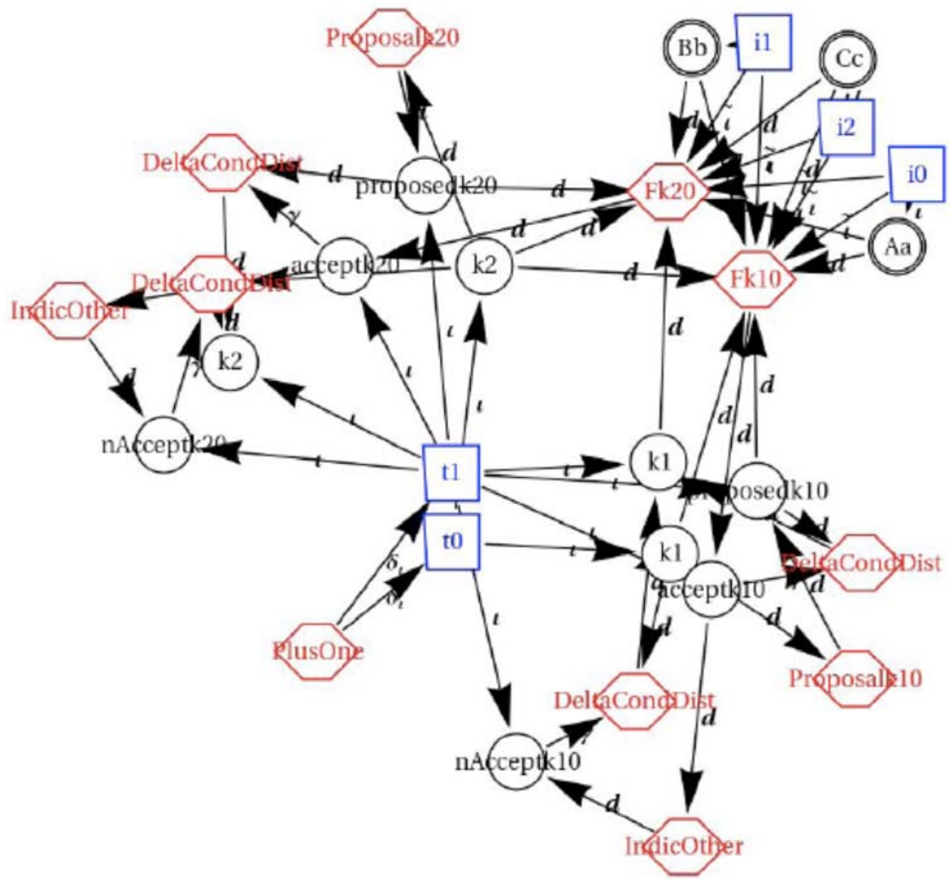
- Advances
  - Enables general formulation of vbl-structure systems



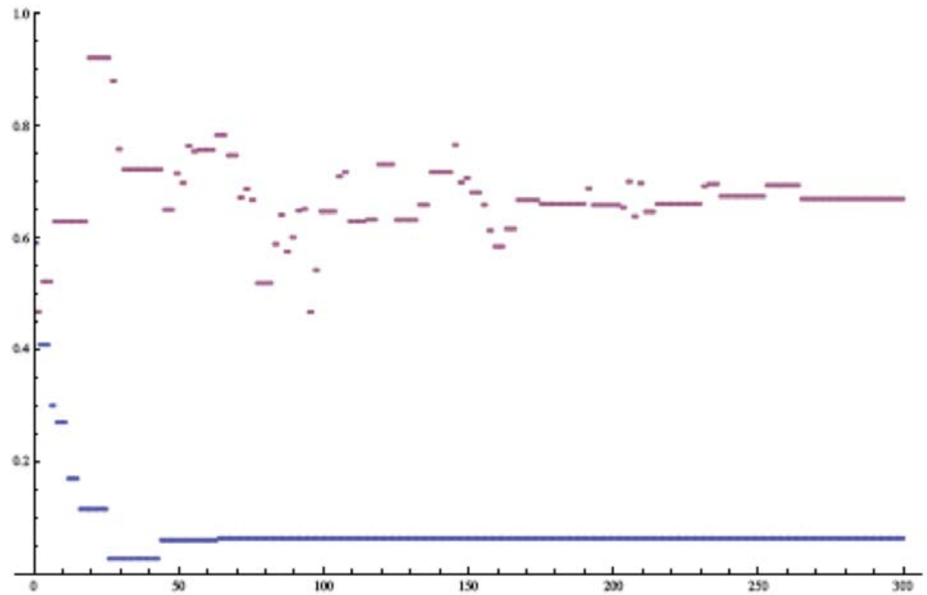
Eg: Reaction network

$$p_1(A_{i+1}|A_i, B_i, C_i, k_1, k_2) = \mathcal{N}(A_{i+1}|A_i - A_i B_i k_1 \tau + C_i k_2 \tau, \sigma)$$
$$p_2(B_{i+1}|A_i, B_i, C_i, k_1, k_2) = \mathcal{N}(B_{i+1}|B_i - A_i B_i k_1 \tau + C_i k_2 \tau, \sigma)$$
$$p_3(C_{i+1}|A_i, B_i, C_i, k_1, k_2) = \mathcal{N}(C_{i+1}|C_i + A_i B_i k_1 \tau - C_i k_2 \tau, \sigma)$$



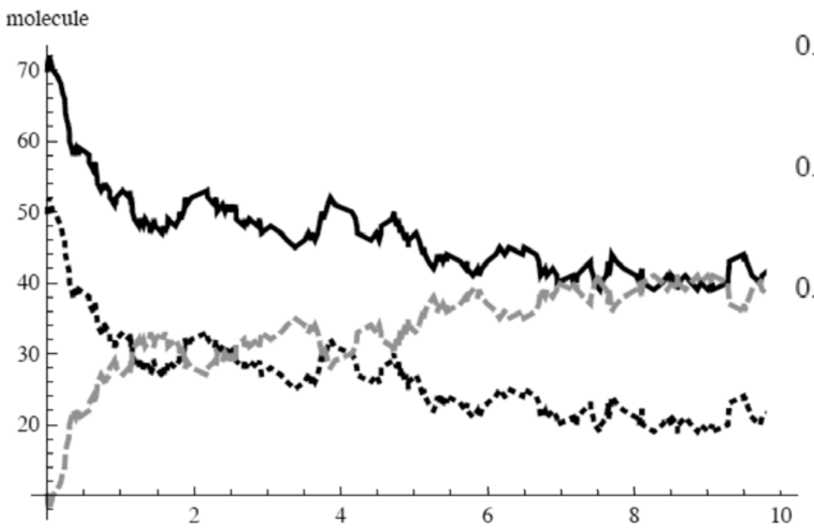

Proposalk20
Bb
i1
Cc
i2
i0
DeltaCondDist
proposedk20
Fk20
acceptk20
k2
Aa
Fk10
DeltaCondDist
IndicOther
k2
nAcceptk20
t1
k1
proposedk10
t0
k1
DeltaCondDist
acceptk10
PlusOne
Proposalk10
DeltaCondDist
nAcceptk10
IndicOther

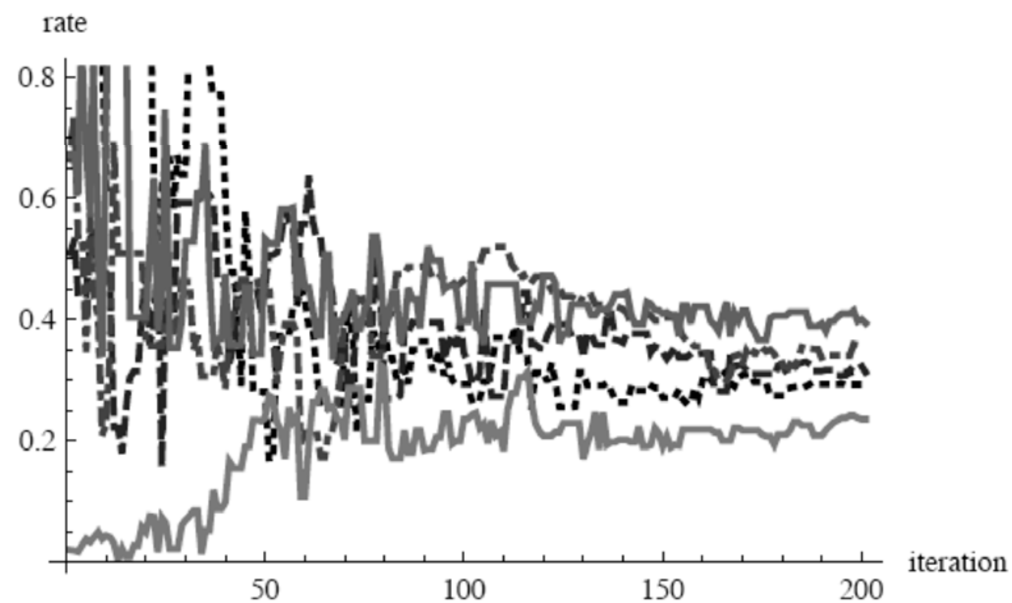
Inference of rates



(b) Sampled parameter values as a function of iteration number.

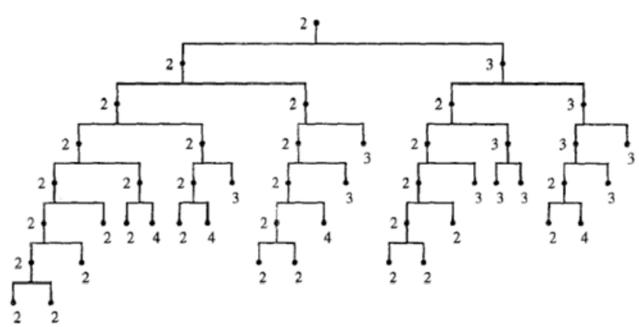
Inference of rates - MCMC mixture of transitions

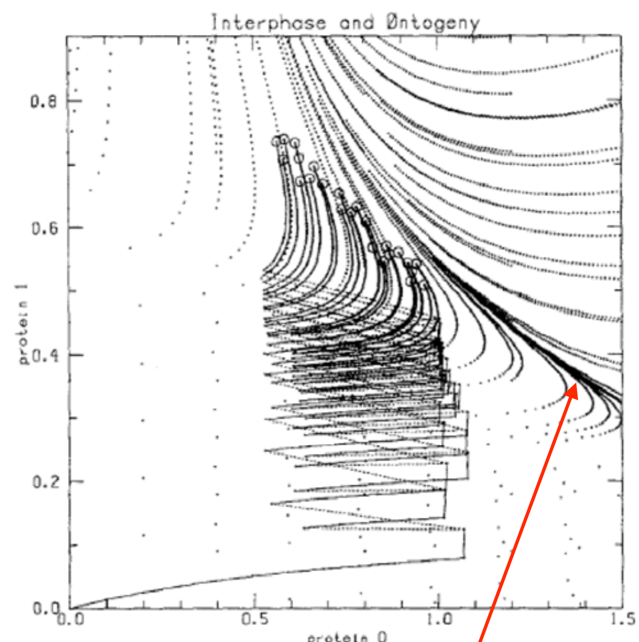




Evolved Dynamics

- Task: GRN-controlled growth
  - grow to 24 cells of 3 cell types
  - stop (or: stop and reproduce)
- State space flow
- Lineage tree
  - emergent grammar





Note separatrix,
a center manifold

Mjolsness, Garrett, Reinitz, and Sharp, in Evolution and Biocomputation: Computational Models of Evolution, Springer LNCS, Berlin, 1995.

Template: Evolver

grammar (continuous-time) *evolver* ($\{\mathrm{organism}(g_i, e_i)\} \to \{\mathrm{organism}(g_j, e_j)\}$) {

$\mathrm{R1}: \mathrm{organism}(g_1, e_1) \to \emptyset$ with $\rho_d(g_1, e_1)$

// death: selection by the environment

$\mathrm{R2}: \mathrm{organism}(g_1, e_1), \mathrm{organism}(g_2, e_2) \to \mathrm{organism}(g_1, e_1), \mathrm{organism}(g_2, e_2), \{\mathrm{organism}(\tilde{g}_i, \tilde{e}_i) \mid 1 \leqslant i \leqslant n\}$

with $\rho_h\, C(g_1, g_2, e_1, e_2)\, q(n) \prod_{i=1}^{n} \phi_2(\tilde{g}_i \mid g_1, g_2)\, \varsigma(\tilde{e}_i)$

// heritable variation of $\tilde{g}_i$

$\mathrm{R3}: \mathrm{organism}(g, e) \to \mathrm{organism}(g, \tilde{e})$ with $\rho_e\, \psi(\tilde{e} \mid e)$

// individual experience

$\mathrm{R4}: \mathrm{organism}(g_1, e_1), \mathrm{organism}(g_2, e_2) \to \mathrm{organism}(g_1, \tilde{e}_1), \mathrm{organism}(g_2, \tilde{e}_2)$

with $\rho_s\, \chi(\tilde{e}_1, \tilde{e}_2 \mid e_1, e_2, g_1, g_2)$

// social interaction

}

Methods

- Semantics:
  - Dynamical Grammars process composition language
- Multiscale methods
- Graph transformations
- Parameter estimation
- Computational Morphodynamics

Computational Morphodynamics

- Model morphology $\leftrightarrow$ regulation, bidirectionally
    - Morphology requires *mechanics, growth, & cell division*
    - Eg. weak spring models coupled to regulation & growth
    - But could be developed much further
        - stochastic, cellular + continuous-space, …
        - Smart & active (lively) geometries & cell complexes
    - Eg. expression domains + growth + mechanics
- Image analysis
- Mechanical modeling
- Define: the study of the three-way interaction of physical, informational, and geometrical processes
    - Thus: molecular mechanisms, regulation, and growth&patterning

Computational Morphodynamics

- Potentially, a new science
  - "How do biochemical and informational processes determine major changes in the morphology of living organisms?"
    (that includes plant animal development, and also metamorphosis and regeneration);
    - A "grand challenge".
  - Other questions as well:
    - "What are the computational consequences of the macroscopic patterns of mammalian brain development?" (neuroscience);
    - "How do living morphodynamic systems evolve?" (evodevo);
    - "How can we design self-fabricating molecular structures?" (nanotechnology)
    - "What kinds of computational processes are best described using morphodynamics?" (computer science based on spatial continuua rather than on Turing machines - a potentially strong engineering spinoff); and
    - "How can one classify morphodynamic systems, up to Turing-computable diffeomorphisms?" (mathematics)
- Leading applications are in biological development

Some *Principles* of Heterogeneous Dynamics

- Integration by *summation* of time-evolution operators
    - Derivation of simulation algorithms
- Graphs → dynamics
- Application to multiscale modeling
- Model analysis, reduction, and understanding
- Abstraction to reusable mini-theories
    - Eg. GRN/ANN, GMWC, RSS, weak springs, …

Methods

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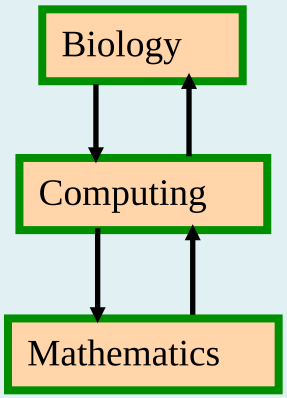
Outline: Math. Methods



- Statistical Mechanics
  - SM in metabolism, transcription
- Stochastic Dynamics
  - Operator algebra
- Classical Spatial Dynamics
  - Hybrid systems; elastic dynamics
- Computational Dynamics
  - Semantics
  - Computational Morphodynamics

Further conclusions

- Dynamics is important & tractable
  - Heterogeneous dynamics required in biology
  - Processes composition: operator addition
  - Algorithms for simulation and learning
- Examples:
  - central metabolism, signaling, development
- Solid foundations exist for a science of "computational morphodynamics"
  - Mathematical, computational
  - Botanical and biological

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http://www.computableplant.org

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- For further information
  - www.ics.uci.edu/~emj
  - www.computableplant.org
  - www.sigmoid.org